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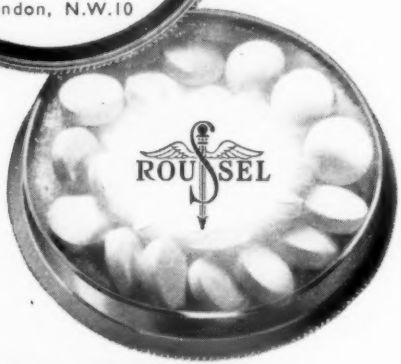

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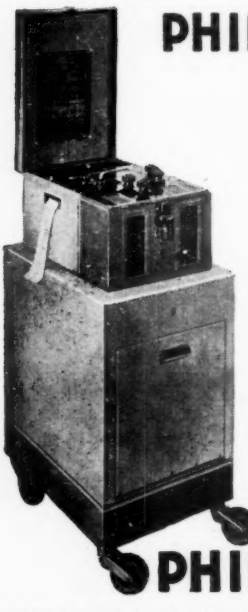

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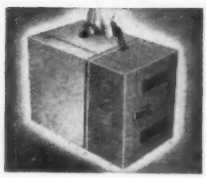

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Proceedings of the Royal Society of Medicine

Vol. 47
385

Section of Physical Medicine

President—DORIS BAKER, M.D., F.R.C.P.

[*January* 13, 1954]

Psychosomatic Preparation for Childbirth

By W. C. W. NIXON, M.D., F.R.C.S., F.R.C.O.G.

THIS paper deals with some aspects of a type of education for expectant mothers which has caught public attention to a considerable extent in recent years. There are now many varieties of it but all include some explanation about childbirth and a good deal of physical training in which certain exercises are nearly always included. It is the side of the preparation which is particularly the concern of the Physical Medicine Section, but the more we examine it the more we see that, though some effects may be purely physical, a great many of its benefits could be attributed to associated mental changes; at the same time we find that the mind-body partnership can sometimes be approached more effectively through bodily action than through complicated mental processes. We are familiar with the idea of the interaction of psyche and soma; in this field of study it is almost impossible to separate them. It is this fact, incidentally, which has made research into particular methods so difficult.

Although "preparation" in the sense that it is used in this title is generally taken to mean some form of treatment of expectant mothers, it is obvious that this is really not more than an emergency measure, a patching up of a situation already well established. This important point is sometimes overlooked and there is, unfortunately, not time here to do more than remind ourselves in passing that preparation begins in young girlhood, even in babyhood. It might then be possible to modify the shape even of the bony pelvis, in the way that Dr. Kathleen Vaughan (1937) suggests. It is then, also, that the pattern is set of the future mother's attitude to child-bearing and all it implies. The gymnastic exercises given in schools for girls might very well be reconsidered in the light of their future functions as mothers, as might some of the sex education that is given.

Returning to preparation during pregnancy—what can be done for the mother at this time? A claim made by many of the schemes of antenatal training is that of increasing mobility of the pelvic joints. Some authorities feel that towards the end of pregnancy joints are sufficiently loosened by the action of relaxin—sometimes too much so. However, it is an advantage for the mother to be familiar with the positions and movements she will have to use during labour. An example of this is the "lying squatting" position which she may have to assume repeatedly during the second stage. There are some additional positions and movement that can be carried out during labour which may give the mother considerable relief if she is permitted to use them, and it is helpful for her to know about them beforehand. Other than this there is no clear evidence of any direct effect upon the actual labour of antenatal exercise designed for loosening her joints during pregnancy.

Another claim is that of increasing the elasticity of muscles especially, of course, of the perineal muscles, but here again it is difficult to prove much direct physical effect upon labour of exercise during the antenatal period. The incidence of lacerations is not reduced. Practice of perineal contraction and relaxation (apart from preparing for the puerperium) does, however, make the mother conscious of functions which tend to be suppressed and increase her ability to co-operate during the delivery, thereby increasing also her feeling of security and satisfaction.

Of what then can we be certain? One of the easiest things to show is the immediate benefit to the expectant mother of teaching her how to adjust her posture to her changed weight balance. Not only is backache quickly reduced but the mother becomes aware of greater ease and grace and gains confidence from this. Then it seems fairly clear that preparation beforehand enables the mother to learn more quickly during the puerperium how to restore her figure and muscular tone—a matter, I am glad to say, on which the modern mother is learning to pride herself. Those exercises intended to loosen her joints do at any rate free her from the compulsion to hold herself rigidly. Many women still become nervous about using their bodies when they become pregnant and are greatly relieved when they find that, on the contrary, it is regarded as a good thing that they should move their bodies easily and freely.

Two skills whose use during labour can be of immense value are controlled breathing and relaxation. Certain types of breathing are helpful in themselves—for example, the deep abdominal one for the first stage—but, in addition, control of breathing is a powerful aid in achieving poise. Physiologists seem unable to give a satisfactory explanation for this, but it has been known for many centuries.

The subject of relaxation is a study in itself. We are all familiar with contributions such as those of Jacobson (1929), and Read's (1933) application of the principles to labour. Simple voluntary relaxation, in quietness, with the inevitable accompanying changes both somatic and psychic, is essentially a "not doing", and is best taught by preliminary education in what "tension" really feels like. Relaxation during pain is not quite the same thing as relaxation in its absence, though it includes recollection of it. It is partly a detachment from the pain but not a dissociation from the body in the sense of losing responsibility for it. It is more a choice and direction of the body's reactions. Relaxation is a matter needing more study, more attention from specialists of both physical and mental medicine.

There is no question, however, that its practice produces various beneficial results, including raising the threshold of experience of pain. To gain the most from this technique a good deal of practice is needed and those who have, in one way or another, made use of it previously—dancers, for instance—gain the most benefit from it. It is part of an attitude towards the body which is one of the chief contributions of people like the physiotherapists, whose approach to their patient's "mind-body" entity is through helping her to understand her body, control it, use it, establish friendly relations with it, to regard it as a creature with which they can work happily, and which is neither to be allowed free rein nor yet driven on the curb. It is fascinating as the classes proceed to watch the changes in some of the mothers, who begin by being nervous of their bodies. To be of the greatest value the physical training must be closely linked with explanations about the birth processes, the purpose of them, how the mother will feel at various times, and what she can do to help herself at these times. It is possible that physical relaxation alone, if practised long enough and thoroughly enough, will help the mother sufficiently, but for the average mother, met for the first time only in pregnancy, it is far more effective to make use of all practical methods of approach. And for the same "average" mother the success of these methods depends upon their being understood by her attendants in the labour ward.

This cannot be stressed too strongly. It is true that adequate preparation during pregnancy will not only make the mother fitter and happier then but will enable her to do better during labour. But it will be remembered that at no time in her life is a woman so vulnerable as during labour. A wrong word here can undo months of teaching; right words can change the whole direction of a woman's attitude. She is more accessible, especially during the earlier part of labour, when she will readily accept explanation and instructions and can be taught simple techniques of breathing and relaxation. Really good treatment in the labour ward is more important than any antenatal training. If I may suggest in what good treatment consists it is in allowing the natural resources within the mother to work as fully and usefully as possible. It means reducing difficulties and obstructions in the mother and her surroundings which impede natural progress, as well as directing her faculties so that they are exercised most usefully. It does not mean imposing one's own views upon her—either by exhorting her to behave according to some preconceived standard or by blaming her if she behaves differently. Both of these treatments can inhibit labour.

Once again I suggest the possibility that a woman who has from girlhood been conditioned naturally for motherhood might be more independent during labour; those who have not, depend very greatly on moral support from the labour ward attendants who should have not only the wish to be kind but some understanding of certain patterns of human behaviour and the means, mental and physical, by which they can, if necessary, be modified.

And what is the result of all this? A mother whose memory of labour gives her deep contentment. It is not true that memory of labour is all wiped out. Details may be, and delight in the child may over-ride other feelings. But in a woman who has been wrongly handled in labour sensations of resentment or guilt can remain as hurtful recollections, even though usually suppressed.

There may result, but only rarely, a painless labour, but great harm can follow false promises of this, whatever the scheme of preparation. Pain should be reduced to the minimum, for it clouds the mother's experience, and one day, who knows? we may be able to abolish it. But again and again we have seen that physical pain is soon forgotten; mental pain may never be.

The ways in which this type of antenatal education should be given are usually through the medium of classes—which themselves have therapeutic value. It is extremely important who conducts these, and it seems to me that two kinds of person are qualified for this work. The first, of course, is the one (doctor, or more usually, midwife) who will be attending, or responsible for, the mother during labour. He or she should give the descriptions and explanations of labour. In hospitals there is not the same continuity as there is in domiciliary practice, but we are glad to find at University College Obstetric Hospital that it is possible for a team to inspire the same sort of confidence as a single person can, so long as the mother senses a unity of aim. The sister-in-charge of the labour wards gives a good part of the teaching, and all her midwives are encouraged to watch classes so that the

principles behind them can be applied in the labour ward. It is obviously essential for success that there should be complete agreement between antenatal teaching and labour ward management. Another advantage, sometimes overlooked, of the Sister taking part in the teaching is its great educative value to her. She will steadily learn more about the reactions of women in pregnancy and labour and become better equipped to deal with them. The same holds very true of the doctor.

The other kind of person who can contribute to antenatal teaching is one who is trained in physical education, who can bring to the work some of the qualities we have discussed and who is able to detect and correct mistakes in performance. We should not, because we see the close psychological implications of this work, underestimate the contribution of the physical approach. Such a person has usually also had training in class work, which is an advantage. She must have special experience of obstetric work and be in close touch with the labour ward where the mothers she trains will be delivered. This is absolutely essential.

In my own hospital, the whole scheme is co-ordinated by a member of the medical staff, working under my direction. This appears to me to be the best way of unifying an effort that is still only experimental and can be beset by many difficulties. I believe that when it is proposed to initiate some such scheme the obstetrician should collect together the people who will be concerned and help them to work out plans between them; and as the scheme develops get them to meet at intervals to discuss and pool ideas. This might save much unnecessary and wasteful effort. And here I would like to acknowledge our indebtedness to the late Mrs. Helen Heardman, who initiated our scheme.

Childbirth bears a needless burden of pain and unhappiness, and we can cure this only as we learn to understand its causes. The problem is being tackled in many ways. Here is one. In centres such as ours the work is experimental as well as being of immediate help to the mothers. In country districts, where matters are more of a family affair, the problem may be easier. In one, at least, a physiotherapist with special experience in obstetrics is teaching midwives how to give some simple antenatal training to the mothers they will deliver. This arrangement can give happy results. What appears to us unjustified is the setting up by some local authorities of "antenatal exercise classes" run by Health Visitors, who do such excellent work in the field of Public Health, but who are often given no opportunity for discussion with the midwives who will deliver the mothers, and who cannot even offer the advantage of any special understanding of physical training. They can give perfectly nice little talks about anatomy and physiology and hygiene, and instruction in various bendings and stretchings that will help to maintain suppleness. All quite useful. But do not let us ever pretend to a mother that such an arrangement will give her "natural childbirth".

The phrase "natural childbirth" which is now so often used is in some ways misleading. It is natural to bear children, but the process in civilized countries is not as nature intended, and when left unaided can deviate still further from the natural pattern. On the other hand, the attempt to convert it into a mere surgical operation brings fresh problems in its train. Perhaps what is meant is that we wish to release nature from the restrictions and difficulties with which we surround her. We cannot return to the simplicity of the completely primitive "natural childbirth"; we do not want to because the civilized woman's capacity for experience is so much greater. And when her complexity is allowed to follow more nearly the natural pattern the result gives her a richness and fullness of experience denied to her primitive sister.

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The Present Practice of Exercises in Ante- and Postnatal Management

By DONALD WILSON, M.R.C.P.

PATIENTS referred for ante- and postnatal exercises usually fall into two groups: Those requiring treatment for low back pain and those requiring treatment for either prolapse or stress incontinence. In 1946 and 1947 I had a considerable number of patients referred for the latter conditions, and the number was sufficient to warrant special sessions being allocated for the treatment of these disorders. In 1951 and 1952 there has been a great reduction in patients who have been sent for the treatment of these conditions. Some reasons why it is not possible to compare these years are as follows:

1946–1947 were immediate post-war years and in spite of every effort, maternity patients were not able to have the amount of care that was available in later years. To take two items, transport facilities were greatly reduced; the difficulties in housekeeping were increased.

1949–1952, the period in which the patients were pregnant showed great improvement in both these items.

Although there has been a drop in the number of patients receiving treatment for weakness of the pelvic floor, there has been no appreciable reduction in the number of patients being referred for postnatal backaches where no gynæcological cause for the pain can be ascertained.

In obstetrics, exercises are encouraged at present both in the ante- and postnatal periods, though it is only recently that antenatal exercises have been taught to many patients. This attitude can be illustrated by referring to J. B. Mennell's book, "Physical Treatment by Movement and Massage", London. In the editions of this book from 1917–1945 he makes very little reference to antenatal exercises and he was a man who was not likely to miss any point regarding treatment by exercises; in the same book (Third Edition) he gives in detail a course of treatment by massage and exercise for the puerperium. One of the reasons for this apparent neglect was the belief that pregnancy was a physiological process and that, provided the mother and fœtus appeared in good health and in the right position, little else need be done at this stage. Undoubtedly in thousands of cases this treatment was successful particularly if the mother was leading a "healthy" life, but few clinics could give the mother clear directions about this. At the same time in almost all books on obstetrics, there appeared the implication that because of civilization and the resultant mixed breeding, women of culture had great difficulty in parturition, whereas the women of savage tribes undertook the act of parturition almost as easily as defæcation.

Women who live in this country do have quick, easy labours and resume their activities rapidly. A history of any British Army on the march, in the days when camp followers accompanied the Army, always provides several examples.

Antenatal exercises are given in order to ensure muscle tone and control for the athletic exercise of parturition, thus enabling the parturition to be assisted by muscular control and the patient to have a more rapid recovery during the puerperium. To consider for a moment and in the simplest possible way the muscular problem during pregnancy: In a pregnant woman there is a gradually increasing tumour, the pregnant uterus which is above the pelvic floor. The most important constituent of the pelvic floor is the levator ani which has two components, the iliococcygeus and the pubococcygeus; originally the former was designed to produce side-to-side movements of the tail and the latter to draw the tail downwards and forwards between the hind-limbs, but in the erect and tailless mammals, these actions are no longer required and the action of the levator ani is to act as a pelvic diaphragm. The muscle will counteract the effects of raised intra-abdominal pressure when the posture is erect. Thus in a pregnant woman, as the uterus enlarges and becomes heavier, there is probably an increase in the strength of the levator ani. I am informed that during the production of pneumoperitoneum, either contraction of the levator ani or the abdominal muscles will produce a marked increase in the intra-abdominal pressure and I see no reason why we should not assume that the increase of intra-abdominal weight due to a pregnant uterus should not produce a compensatory hypertrophy of the levator ani. In a similar way the abdominal muscles may also respond and I have often been struck by the strength and power of the abdominal muscles in a pregnant woman.

I suggest that the pregnant uterus in itself is the best apparatus for producing the necessary power in the muscles of the pelvis. Exercises are very important at this stage. It is of prime importance to ensure that the pregnant woman is having interest taken in her. Often she is extremely frightened of her inevitable ordeal which is still subject to many "old wives' tales" and superstitions. By attending an antenatal exercise class, she is in the company of women in a similar situation; she is instructed in the art of taking exercise which, incidentally would produce a sense of well-being whether she was pregnant or not, and she is instructed also in the technique of parturition, so that when labour begins, she is experiencing her teaching and not entering in to completely strange conditions.

The second effect of the exercises is the resultant muscle control which will procure improved muscle relaxation. No athlete can compete in an event unless he has learnt to relax during participation and in the same way no pregnant woman should be expected to undertake parturition unless she has been taught how to relax the muscles at the appropriate times. Probably the most important single instruction is the control of the breathing.

Postnatal exercises have been accepted for years as necessary, mostly to bring the abdominal muscles under control in order to restore the waist-line of the patient. As I have suggested previously, in a normal case the waist-line is strong enough to look after itself. The muscles are strong and usually can contract adequately. It is more important to care for the pelvic floor. Early leg exercises have reduced the incidence of thrombophlebitis in medical and surgical wards. Respiratory exercises are also of equal importance. What of pelvic exercises?

It must be remembered that in the later months of pregnancy there has been a relaxation of the sacro-iliac ligaments and a widening of the symphysis pubis. These ligaments do not recover their normal grip immediately and I believe it is possible that early weight-bearing may be a factor in producing low back pain in pregnancy. Have some of these women been allowed to undertake relatively strenuous exercise when the pelvic ligaments have been soft?

In addition, the position in bed may have been unsatisfactory thus producing abnormal strain on a susceptible pelvis. Exercises for the pelvic floor are more difficult to assess; the levator ani is an intra-pelvic muscle and has no attachment outside the bony cage. The diaphragm can be exercised by movement of the ribs but in the case of the levator ani, I am doubtful if movement of the legs will procure a direct action of this muscle, with the possible exception of external rotation of the thigh produced by the obturator and pyriformis muscles. External rotation of the thigh may produce

action of the levator ani because this muscle arises partly from the " white line" of the pelvic fascia which covers the pyriformis and obturator internus muscles. Contraction of the gluteus maximus may produce contraction of a normal levator ani by synergistic action. Increase of intra-abdominal pressure by the action of the abdominal muscles and diaphragm will result in an immediate contraction of the levator ani but if the levator ani has been damaged, then the effect of contraction of the halves of this muscle may be to increase rather than diminish the normal gap in the anterior part of the pelvic floor and a cystocele is then threatened. I suggest that pelvic exercises be delayed if damage to the perineal body has occurred during parturition but if no damage can be ascertained then pelvic floor exercises can be started early. Probably the most efficient exercise to be done at this stage is for the patient when lying flat on her back to carry out deep inspiration and expiration then endeavour to retract the pelvic floor into the abdomen, at the same time rotating the thighs outwards and contracting the abdominal muscles. If it is thought that the pelvic floor is abnormally weakened, then the pelvis can be raised in order to prevent the threat of a cystocele.

An exercise which is performed incorrectly can be harmful. When pelvic floor exercises are given, great care must be taken to ensure that the levator ani does contract; sometimes I see patients who can only tighten the anal sphincter and they have been instructed that this is the correct exercise. In the later stages of the puerperium, intra-vaginal faradism is useful in giving the patient the correct feel of a contracted levator ani. Intra-vaginal faradism does not replace the correct exercise.

In postnatal exercises it is important not to give the mother too many exercises to do because she will not do them unless she has adequate help in the house. I recommend keeping the exercises as simple as possible and then there is a chance of the appropriate exercises being done. Correction of posture is often necessary once the patient is active, but again one must remember the time factor to allow the pelvic ligaments to regain their normal strength.

The present teaching of ante- and postnatal exercises is in a difficult position. The instruction of exercises is essential, but the mothers who are converted to this treatment tend to receive too many, and those who are doubtful about the need receive far too few or carry out the exercises half-heartedly.

I am sure that antenatal exercises play a great part in the rapid recovery after parturition and will in this way prevent invalidism after childbirth; these exercises are largely preventative measures.

Postnatal exercises are more specific in character and can be regarded as curative.

During the past 100 years, intensive study and work has been done to remove the fear and travail of normal labour, but 100 years is a brief moment in the history of childbirth and now that many of the major causes of maternal mortality have been either eradicated or reduced, a great endeavour must be made to overcome the fear of labour and to reduce morbidity due to labour. The introduction of exercises will play its part in this endeavour though conclusive evidence will only appear after a number of years and will only be confirmed by wide-scale surveys.

[*February* 10, 1954]

SAMUEL HYDE MEMORIAL LECTURE

[No. 11]

Physical Medicine

By W. S. TEGNER, F.R.C.P.

MADAM PRESIDENT, I thank you and your Section for the great honour you have done me in appointing me Samuel Hyde Memorial Lecturer. You have also honoured me by your trust in me, which you have manifested by allowing me to choose the title of my lecture. I think, therefore, that I owe you some explanation of my temerity in embracing the whole extent of our specialty and not being content with some single part of so vast a topic. But the fact is that among my ten predecessors for this Lecture there have been those who have been able to expound to us clinical, technical and historical aspects of our specialty, and Howitt (1952) described the development of Physical Medicine in the last few years. This led me to this attempt to review the present state of our specialty, and to scrutinize it critically. It is my frank opinion that some such scrutiny is necessary at the present time, when our specialty is growing so rapidly and attracting so many recruits.

TREATMENT BY PHYSICAL METHODS

Many treatments by physical methods have been outdated, and have passed into limbo; others still linger on, and yet others seem firmly established, and likely to remain. New treatments arrive with a flourish of trumpets; some of these die a quick and unregretted death; others die a slow and unhappy death; others seem to have come to enjoy, if not immortality, at least longevity.

Now, these treatments are very largely prescribed in cases of painful conditions of the locomotor system, and this demands an expert knowledge of the natural history of these very conditions. We should be aware that the classical attack of "lumbago" usually clears up of itself in the majority of cases after a comparatively short period, and we should not blindly accept the disappearance of symptoms to be the result of whatever treatment has been ordered. Long before we knew about prolapse of the intervertebral disc we treated lumbago and sciatica with considerable success. And what is more, many sufferers from these conditions were treated successfully and safely with rest and analgesics alone, and the patients got better. Such facts cry aloud for proper controlled experiment in our evaluation of the results of the treatment we prescribe. There is a tendency in some quarters to decry controlled experiment, but the fact remains that scientific medicine as a whole will, in these enlightened days, accept nothing else as proof of the efficacy of any form of treatment, whether by drug, antibiotic or electrical current. It is of no scientific value whatsoever to say "my patient suffered from fibrositis, I treated him with the low frequency current, and after two weeks he got better". In scientific medicine *post hoc* is not the same as *propter hoc*. Although I have heard in this very Society a claim made that the controlled experiment is not necessary to substantiate the validity of a claim to the efficacy of a treatment, it is most refreshing to note that this lesson of the controlled experiment is so well understood among our younger colleagues, who take it as a matter of course that they must substantiate their claims in this way.

In Physical Medicine we deal with many treatments, such as electricity, which exert a strong suggestive influence on the patient; massage and heat, for example, can be very pleasant, and both these factors will tend to make the patient attribute efficacy to the treatment which is being employed. It strikes me as the height of folly to prescribe for a self-limited disease a pleasant suggestive form of treatment, and then ascribe the subsequent improvement in symptoms to the treatment. I believe it to be our duty as specialists in Physical Medicine to sift out the many extremely valuable forms of treatment of which we should be masters from the dross of expensive, time-consuming but useless manœuvres which may be superficially popular. And I believe that it is because of an understanding of this duty that our specialty is undergoing such rapid growth. The medical profession looks to us to enlighten them on the value in medicine of physical agents, and we must not fail to accept this task in a true scientific spirit, unobscured by mystery, suggestion or the blind acceptance of time-worn tradition.

I would now like to examine some of the forms of physical treatment which are considered to be particularly within the scope of our specialty, and will start with massage, which has been so widely regarded as being one of the mainstays of Physical Medicine, and the prescription of which used to be considered almost a duty of the Physical Medicine specialist. The claims made for the effects of massage are legion, but many of the conditions for which it is advocated have disappeared or are disappearing from current pathological concepts. While I myself believe it has a certain limited value, particularly in trauma, I also believe it to be expensive and time-consuming—in fact, a luxury. It is very difficult to find any really scientific investigation into the effects of massage; its powers seem to be traditional, and to be accepted without question from generation to generation. It is traditionally claimed that it is a powerful stimulus to the circulation. But Ebel and Wisham (1952) investigated this claim in an admirable controlled experiment, using both estimations of muscle temperature by means of thermocouples and estimations of clearance of radioactive sodium from the muscles into which it had been injected as their guides; they found no evidence at all that massage caused an increase in arterial circulation. But this paper did not attract the attention it deserved, and apparently it is convenient to neglect it. More popular, apparently, are such claims as those reported in *The Times* of October 27, 1953, in which we are told that Russian scientists are not very impressed with the work being done outside Russia on immunity to the common cold, preferring the researches of Professor Tarkanov, who says that the way to build up immunity to this condition is by means of massage and cold baths. The enormous number of patients who ask for massage and the similar number of doctors who prescribe this luxury should be a stimulus for a scientific investigation into the validity of the claims made for it.

Electricity

The electric current is a convenient and usually readily available source of energy for the working of much of the machinery which is to be found in departments of Physical Medicine. Unfortunately this has encouraged the belief in the lay mind that this mysterious force, electricity, is the prime factor in the various treatments for which electrical energy is utilized. How often do we have patients asking for the "electrical treatment"! So many of them feel cheated if, when they come to our departments, they do not automatically get massage and electrical treatment. How valuable is the direct current in therapeutics? Various claims are made for it that it is soothing, stimulating, and that it can shift œdema and exudates. Certainly the controlled experiments of Millard and Wynn-Parry (1953) on its use in the treatment of effusions of the knee-joint did not substantiate the claims made as to its efficacy in this condition. Certainly there are very many of our orthopædic colleagues who see many cases of synovial effusions and traumatic exudates who seem never to have heard of the wonders of the direct current and who do not ask us to lay it on. Certainly Ritchie, speaking

in this Section, deplored the waste of time and money which resulted, in his opinion, from the pointless use of such treatments, and I am sorry that his paper was never published.

Then there are the various forms of ionization for which so much is claimed. I notice that there is a tendency for such treatments to be less and less prescribed, and certainly it has been my experience that very little positive evidence of the efficacy of such manœuvres as salicylate or iodine ionization can be obtained. Certainly I have found that it is generally quicker and easier to give these drugs by the mouth or by hypodermic injection. In the case of penicillin, a preparation which certainly can be introduced electrically, I think everyone will agree that it is quicker and easier to inject it intramuscularly and let the blood stream carry it to where it is most needed.

I have consulted ear, nose and throat surgeons and asked them if they still hold certain ionizations of mucous membranes in high esteem, and have met with the answer that they felt it was the preparation and cleaning of the mucous membranes prior to the ionizations that really mattered, and that ionizations were no longer considered very important. Histamine and similar preparations with similar action are still frequently used. Certainly startling effects can be produced with this treatment, but personally I wonder if equally good vasodilator results, if they are really necessary, could not be obtained by other simpler methods, and if the results which are claimed for this form of treatment may not depend to some extent on the power of suggestion. There may be some value in ionization; it is our duty to understand its technique, but also to regard it scientifically and, if necessary, sceptically.

We still see and hear of the use of the sinusoidal current in treatment. I think that there is very little indeed which can be said in support of this current as a therapeutic agent. Probably its effects are purely suggestive, and unless controlled experiments can be produced which will convince me that it produces positive effects better than anything else, I will adhere to the view that we should relegate this, with the high frequency discharge, to the limbo of treatments which have "had their day and ceased to be".

The story of the faradic current is of great interest. It has the advantage of being readily available from simple portable machinery, of being easily applied, and of being a powerful agent of suggestion. It achieved a great reputation as a means of building up muscle, and it was thought that all that was necessary in resuscitating a patient's quadriceps after they had wasted was to strap him up with a source of faradic current and an automatic surger and let the current do the work while the patient read his newspaper. To me, in these enlightened days, this is a horrible sight, and I believe we are right in the opinion that the faradic current cannot be expected to play any more than an educative role in the guidance of the patient in how to use his own muscles. I therefore welcomed Millard's (1952) paper on the use of faradism as a muscle builder compared with other treatments.

In the matter of ultraviolet light irradiation we meet an instance of a form of physical energy which was at one time essential and specific for the treatment of lupus vulgaris. There can be no question that this form of treatment once proved its value beyond all doubt, and brought relief to many unfortunate sufferers. But recently, as we all know, there have been two important developments, one that the tubercle bacillus is neither so liable to attack nor so successful in attacking the human skin, and the second that new preparations, more easily administered, such as calciferol and isoniazid, seem equally, if not more, efficacious. I have noticed a tendency among some people to deplore the fact that local ultraviolet irradiation is not now being frequently prescribed for lupus. Surely this is a silly attitude? We can pay due homage to the pioneers who produced a magnificent treatment for a hitherto intractable disease, and welcome the advances of science and hygiene which have enabled us to reduce the incidence of lupus and treat it much more easily and conveniently. I agree that local ultraviolet irradiation can be of help in the treatment of a variety of indolent ulcers and skin conditions, but I do not think it is specific or essential for any of them.

Personally I have little regard for claims about the necessity of general ultraviolet irradiation. There is no proof that these rays are "tonic" or that they confer immunity against infection. Those of us who are fortunate enough to be able to disport ourselves on the top of Swiss mountains in the middle of our murky English winter come back fit, bronzed and handsome, but, having lived for some weeks in the uncontaminated air and pure sunlight, we are far from being immune to the bacteria and viruses of our own land, and almost invariably go down with a severe cold in the head on returning to England because we have lost, not gained, immunity. Similarly, to talk of ultraviolet irradiation as being the treatment of election for rickets is sheer nonsense; Vitamin D is more quickly effective when doled out by the spoonful than when slowly elaborated in the skin. I must confess that I find the carbon arc lamps in my Department a useful placebo and waste receptacle for patients who seem to want the comfort of some harmless, non-specific treatment, but I prescribe this treatment with full awareness of what I am doing.

At this point I wish to digress a little and protest against the jargon which is sometimes used to fog our specialty. One hears of the "tonic" properties of ultraviolet irradiation as though this were something specific instead of a general term which seems almost indefinable and delightfully vague. Apparently a dose of iron and gentian, a cold bath and an ultraviolet irradiation can all be "tonics"! Similarly, we hear so frequently about "metabolites and waste products" and their removal. The physiologists tell me that lactic acid or carbon dioxide and water can result from the combustion of glycogen and that certain end-results of protein metabolism can be found in the blood stream, but

that these are all adequately dealt with by normal metabolic processes of the body. To talk glibly and pseudo-scientifically about "waste products and metabolites" is about as useful and out-dated as talking about ptomaines. Similarly, we use far too many misleading terms and eponyms about the various currents we apply. We talk of the constant current, the direct current, and galvanism all meaning the same thing. Such phrases may mystify our patients and impress the uninitiated, but do we really wish to be mystery men or witch doctors? Unfortunately, the use of jargon has invaded and obscured the next therapeutic physical agent which I wish to discuss: that is heat.

Heat

There can be little doubt of the value of heat in treatment. We know how it produces a vasodilatation and is at the same time, under certain circumstances, soothing. We know that it produces changes similar to those of inflammation, which is defined as the reaction of tissue to injury. It is probably the most valuable single physical agent in therapy. Unfortunately heat, too, has been obscured by a layer of jargon and obscurity. Some talk of infra-red irradiation and of radiant heat as if they were different forms of radiation and not fundamentally the same—a useful surface heat. We use the phrase short-wave diathermy, and in prescription it is essential that we do so, but we must not compromise with those that ascribe mysterious powers to rays of these wave-lengths. The history of the introduction of short-wave diathermy as a therapeutic agent is one long object lesson to those who wish to apply a new physical principle to therapeutics. How well I can remember the long papers emanating from the continent of Europe in the early days of short-wave diathermy. These gave long lists of conditions without pathological basis such as fibrositis, myalgia, myositis, fasciitis, lumbago and torticollis, and claimed wonderful results in them all. It became the craze and panacea; everything would respond to short-wave diathermy and its mysterious effects. But how nauseating these papers appear in 1954. When once we accept the simple principle that short-wave diathermy in skilful hands generates a useful heat at the point where heat is needed we are in possession of a most reliable and useful weapon in therapy. This is a lesson we have learnt, and its value has been shown in our attitude to the subsequent introduction of ultrasonic waves as a possibly useful therapeutic agent. In short-wave diathermy we have a useful source of heat which I have said needs skilled hands to use, and I think our specialty is much indebted to the work of such as our friends Bauwens and Scott (1953) and Scott (1953) for their papers on the techniques for obtaining the best results with this form of treatment, for, as I have already said, we must be prepared to act as scientific advisers to the rest of the medical profession on the application of these physical agents. When the so-called micro-wave diathermy was introduced into this country there was, fortunately, no ugly rush to get in first with this new form of mystery treatment, and the work of Boyle and his associates (1950, 1952) showed that Physical Medicine specialists could take a new form of treatment and analyse it from the point of view both of correct physics and techniques and of therapeutic value.

In the story of ultrasonics applied to treatment, I think Physical Medicine in England and America has shown that it can learn its lesson and act scientifically. As the Germans had been left with large quantities of ultrasound generators on their hands after the war—for they had tried to use these waves for aircraft detection—they tried out various ways of getting rid of them, and one was on the public as a powerful new therapeutic weapon. This weapon was accepted with delight by the practitioners on the continent of Europe, who started all over again with their claims for miraculous cures of fibrositis, myalgia and all the rest. But the paper by the Council on Physical Therapy of the American Medical Association (1952) showed that our colleagues in the United States were taking a very serious look at this new-fangled means of treatment, and pointed out many of its potential dangers. We in England had learnt our lesson, and the Ministry of Health asked certain members of our profession to investigate the claims of this form of treatment, an investigation which prevented the wholesale importation of ultrasound generators until the claims of this form of treatment were duly scrutinized. There was no spate of publications from this country on the miracles of ultrasonics, and it seems to have been carefully scrutinized, found wanting, and allowed to die.

Electro-Diagnosis

But one of the most important spheres with which the Physical Medicine specialist is connected is that of electro-diagnosis. We were all brought up on the use of faradism and the interrupted direct current as the method necessary for assessing the state of the neuromuscular complex. I remember medical students of my day vainly attempting to master and memorize the mysteries of A.C.C. and K.C.C. Owing to the work of such of our colleagues as Bauwens (1950), of Richardson (1950), of Ritchie (1948), and of the Air Force Group, the whole technique of electro-diagnosis has completely changed, and a mine of information on the pathology of myopathies and neuropathies has been unearthed. Modern developments in electro-diagnosis have brought Physical Medicine into close contact with the physiologists and neurologists, and have opened a fascinating field of research before them. It has been said that intensity duration curves, the modern development of "faradism and interrupted direct current" are sufficient for our purposes of diagnosis and prognosis,

but I am one of those who feel that if we do not go ahead and accept the opportunity to be at the forefront in this wonderful new opportunity for research, we will be throwing away a golden opportunity.

So far, I have examined with a somewhat ruthless scrutiny the methods of treatment which are often popularly thought to be the be-all and end-all of our specialty. This attitude of scientific evaluation is, I know, shared by my colleagues. Yet in spite of this attitude our specialty is making great strides, is being encouraged to train young men to meet the demand for specialists in Physical Medicine, and is attracting recruits from other branches of our profession. I am wrong, therefore, in saying that this is in spite of our attitude; it is because of our attitude. For Physical Medicine found that, not having to rely for treatment on drugs or the knife but having the dynamic forces of nature within its sphere, it had to study the effects and importance of muscular activity. It had to study the abnormalities of muscular function and their restitution to normal. We are all aware of what great strides were made in this connexion during the war, when Physical Medicine specialists were given an opportunity of taking over control of restoration of physical fitness. Till then it had been widely held that massage, passive movements and passive treatments, and individually applied remedial exercises were all that were necessary in this field. But our opportunities taught us that we were straying far from the truth, and that passive treatment and monotonously repeated isolated movements were often harmful rather than beneficial. Much of the present success enjoyed by Physical Medicine is due to the fact that our specialists have insisted on clearing space in our departments by throwing out outdated electrical apparatus and massage couches, and seeing that our patients are now expected to take a leading active part in their own treatment. My own advice nowadays when I am consulted about new departments is that space for activity is more important than apparatus. In our modern hospitals the staff of the Departments of Physical Medicine can see that restoration of activity does not start when the patient is given that horrid label convalescent, but that training for recovery can take place while the patient is in bed. The spread of this gospel of activity has led us into the fields of restoration of optimum function and resettlement. The work done by Cooksey in guiding the disabled housewife has made King's College Hospital a sort of modern Mecca! We have learnt that restoration of function is no matter of exercises done, that the psyche of the patient must be stirred by suitable environment as provided by the group, and that training and education are part of our work.

I know well that here I am preaching to the converted, but a review of this sort demands a positive statement on this subject; for activity and its prescription and guidance has now become the main therapeutic part of our specialty.

In this connexion it is interesting to consider the present situation regarding hydrotherapy. While abroad on the continent of Europe the spas still seem to moulder on in a mediæval atmosphere, where they boast of the imaginary benefits of their nauseating sulphurous muds or their bitter chalybeate waters, and treat their unfortunate victims by the strong suggestive powers of their douches and packs, in England the spas have not been slow to examine the claims of hydrotherapy with a scientific eye, and to establish these modern centres for the treatment of sufferers from poliomyelitis and the painful diseases of the locomotor system which play an important and rational part in modern therapy. One of the parents of this Section was the Section of Medical Balneology and the parent has grown up with the child!

Diagnosis

We in our various departments receive patients from a wider variety of sources than any other medical specialty. Because of the modern concepts of restoration of function almost all of our colleagues call on us to help them in restoring their patients to activity. We are therefore, perforce, Jacks-of-all-trades, and see a very great variety of medical material. This both demands and fosters experience. This wide scope has necessitated the long and difficult apprenticeship which now faces those who wish to take up our specialty. I have met some who have suggested that they are content to be specialists in treatment. This seems to me to be unambitious, lazy, and altogether unworthy of us. I was particularly struck when, on hearing a speaker make this amazing claim, he went on to say that he was amused by the number of occasions on which he had to review the diagnosis made by the referring physician in view of his own experience. He stood condemned by his own words; he showed that in spite of his own statement he was being forced to diagnose.

It is natural that much of our work must centre round painful disease of the locomotor system. We should, if we accept our opportunities, become expert at the diagnosis of these diseases. No one who takes care of large numbers of chronic and incurable arthritics should fail to acquire an insight into the natural history of these diseases. If he uses his opportunities he should become an expert, not only in their management, but in such matters as prognosis, complications and influence of various extraneous factors in the disease process. He will thereby become far more competent to guide the patient than those who are less experienced, but are willing to prescribe the fashionable treatment of the moment for the odd case they meet. The care of the arthritic is no matter of mere prescription, but of long-term management, and who is better fitted to assume this responsibility than the experienced and properly qualified specialist in Physical Medicine?

Conclusion

We specialists in Physical Medicine are now faced with a challenge. Doubts have been expressed about our fitness to diagnose; doubts have been expressed about the extent of our field; and other specialties consider that they are capable of covering much of our ground. Our present attitude of demanding the highest standards from our recruits, and of being satisfied with nothing but the best, has enabled us to meet this challenge, and to answer the call for the expansion of our specialty. We cannot afford to rest satisfied with the pronouncements of our fathers, or placidly to rely on time-honoured theory. We should be smitten with an insatiable thirst for scientific knowledge. We should encourage in our apprentices a healthy scepticism and criticism. They should not be forced to accept the ideas of their elders as dogma, with an unquestioning faith in what has been handed down by tradition. It is our duty to encourage them to indulge in research, and to control their investigations so severely that their results satisfy those hardest of taskmasters, the statisticians. All this will demand from them much more than the mere running of sessions for the prescription of physical treatment. It demands time for thought and reading, and it is the duty of the seniors to afford them this time, even if we have to do a large share of the routine work ourselves. The high road of success lies open to our specialty; let us not be sidetracked.

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Section of Urology

President—HUGH DONOVAN, M.B., F.R.C.S., F.R.C.S.Ed.

[*January* 28, 1954]

Urethroplasty in the Treatment of Strictures

By JOHN SWINNEY, M.C., M.S.

My experience of reconstructing the urethra is based on the technique which I described in the *British Journal of Urology*, 1952, **24**, 229. This method, which is dependent on the preliminary removal of all diseased tissue, is particularly applicable to severe stricture of the urethra where fistulæ have tracked into the surrounding tissues and perhaps caused abscess formation and fibrosis extending from the perineum to the penis. The method may also be applied to other diseases of the urethra which require radical surgery.

The whole of the diseased urethra can, if necessary, be removed from the external meatus as far back as the membranous urethra. To approach the urethra for this purpose a mid-line incision is made for the required distance along the median raphe of the penis, scrotum, or perineum, and the skin edges are separated and undercut. The incision made, however, encloses the openings of fistulæ, and once the skin edges have been retracted all fibrosed and infected tissue is dissected down to the urethra, and in the scrotal region the testes are separated by complete division of the scrotal septum to allow adequate exposure. The fibrosed tissue, together with the requisite length of the urethra, can then be removed. The resultant raw area is then covered by suturing the skin edges in the mid-line, anchoring the sutures to the raw undersurface of the corpora cavernosa penis, and, if healing proceeds favourably, a mid-line linear scar should extend forwards from the proximal opening of the urethra either to the distal opening of the urethra, or to the end of the penis if the whole urethra has been removed. Where the urethra has been cut either in front or behind, it is most important to obtain accurate anastomosis of the urethral mucosa to the skin. Occasionally parts of the roof of the urethra may appear sufficiently healthy to be left, and the skin edges are sutured to this on either side.

Once the skin edges have healed the reconstruction of the urethra can proceed, and it is based on the principle that a strip of skin or epithelium, when isolated and buried, forms a longitudinal tube. In this way a strip is outlined extending from the proximal to the distal urethral orifices. The strip is left attached to the deep tissues, but the lateral skin edges are undermined and brought over the strip to bury it. Again, in favourable circumstances, healing of the overlying skin should take place by first intention, leaving a second linear scar covering the epithelial tube which is to form the new urethra. In this way we have found that a useful urethra can be built up allowing the patient to lead a reasonably normal life.

In "Modern Trends in Urology" (1953), edited by E. W. Riches, a rather similar technique is described by Bengt Johanson on p. 344. He splits the urethra along its ventral aspect backwards as far as may be necessary to divide the stricture, and then sutures the skin edges to the exposed urethral mucosa. When healing has taken place a strip of skin and epithelium is buried to form a new urethra—as in the Denis Browne operation for hypospadias. In dealing with the scrotal urethra Johanson draws the skin of the anterior surface of the scrotum backwards underneath the scrotum, and fixes it to the cut edges of the urethra to repair a stricture in the bulb. The scrotum is not split.

Using the method I have described, I have operated on 19 cases (Table I). These cases were chosen for their difficulty so that the operation could have a severe trial.

TABLE I.—URETHROPLASTY

Total number of cases	19
Good results	16
Required secondary repair of fistula	2
Broke down; ended as suprapubic cystostomy	1

Our experience of urethroplasty is, on the whole, fairly satisfactory. We have found several practical difficulties which need some description.

Firstly, it is obvious that diversion of the urinary stream is necessary, and in most of these cases a suprapubic cystostomy has been used throughout. In 2 cases posterior urethrostomy was used during the first stage, and a suprapubic cystostomy during the second stage. This may be a better way of draining the bladder than by suprapubic cystostomy in both stages. A Foley catheter brought out through the proximal opening when the urethra has been cut in the bulb, or even in the membranous urethra, helps to get accurate union between the mucosa of the membranous urethra and the perineal skin. It acts as a splint during this process.

In the early cases when the strip was being buried the skin edges on either side were approximated by transfixion with a silk suture held in place by beads and aluminium stoppers, as in the Denis Browne operation for hypospadias. In one or two cases the epithelium grew along one or more stitch holes extraordinarily quickly setting up a secondary fistula, and latterly I have used Michel clips for this purpose, leaving them in for seven days, and I think they are more satisfactory.

If fistulæ have formed during the second stage, either from a stitch hole becoming epithelialized, or as a result of infection in bad cases, it has been easy to excise the fistulæ down to the new urethra and close the skin over it, and no further trouble has been experienced.

It is a little difficult to estimate the optimum width of the strip of skin. On the whole I have tended to cut too wide a strip and the urethra has, accordingly, been a little capacious, especially in the scrotum. This has its disadvantages in that the tube which is not surrounded by muscle has no power to expel its contents as in the normal urethra, and after micturition a little urine may remain in this dilated portion and cause a slight dribble afterwards. This disadvantage is readily overcome by instructing the patient to express the residual urine manually after micturition.

I have had no trouble arise from hair formation in the new urethra. The hair follicles atrophy, and at urethroscopy a few weeks after the new urethra has been in action, the most that has been seen are a few tenuous hair filaments with no phosphatic deposit on them.

A serious difficulty has been the amount of sweating that goes on in the perineum and scrotum, and this has tended to make the skin a little sodden, and in some cases to delay healing. We have found no satisfactory way to overcome this beyond very frequent baths and dressing with dry gauze and boric powder, and infra-red rays.

The interval of time which elapsed between the first and second stages in these cases has usually been four to six weeks. This may be too soon, but when the skin edges are nicely healed at the end of the first stage I have seen no reason to delay proceeding with the second stage.

During the second stage, while healing is going on, it is common to have some purulent discharge from the external meatus. This I believe comes from the granulation tissue on the undersurface of the skin flaps over which the new epithelium grows. It slowly ceases in about ten to fourteen days, and I think it is a good indication that healing has been completed inside, but I do think it is important to prevent the meatus from crusting over with this discharge and so damming up the pus.

We have, for our own satisfaction, urethroscoped these cases several times after operation, and have been fairly satisfied with what we have seen. The epithelium looks almost white and quite smooth, and with, as I have said, a few fine hairs at times. We have passed bougies for our own information in most cases. Sometimes they are difficult to introduce, not because of any narrowing at the junction of the new and old urethra, but because of some irregularity there. Once this has been negotiated the bougie usually proceeds easily.

In some cases which have been transferred to us with a suprapubic cystostomy already established for some time, we have had difficulty with phosphatic stone formation in the bladder, and chronic cystitis, and this is one of the disadvantages of having a long-standing suprapubic cystostomy.

It is a disadvantage of reconstruction of the urethra that it means multiple operations and a long stay in hospital, but the patients we have dealt with have been happy to undergo this after years of frequent dilatation with bougies, and often abscesses and fistulæ. This procedure offers hope to these people, and the ones we have been successful in treating are amongst our most grateful patients.

Mr. Denis Browne thought that the name of R. Hamilton Russell should be mentioned as "the onlie begetter" of these ensuing operations. His technique (1915, *Brit. J. Surg.*, **2**, 375) for the excision of strictures depended on the idea that a strip of mucosa must, if buried, inevitably form itself into a tube. This operation would have had the recognition it deserved if more surgeons had refrained from improving it by sewing the urethra into a tube round a catheter, with the inevitable result of getting another stricture. The technique of Bengt Johanson (1953, *Acta chir. scand.*, Suppl. 176), who was the first to adapt his (Denis Browne's) operation for hypospadias to the cure of urethral strictures, differed from that of Mr. Swinney in preserving the mucosa of the strictured area instead of excising it. In a congenital stricture he (D. B.) had kept the wound open to allow the mucosa to spread and then buried it with good results. He suggested that this variation might be worth trying.

Mr. Thomas Moore said he had found the method simple and satisfactory. Surely, however, there was no need to use an inlying catheter after the first stage? He allowed the patient to pass urine spontaneously through the created hypospadias. Did Mr. Swinney know why Johanson had devised his complicated procedure? Was it because in a very posterior stricture there was not sufficient elasticity of the perineal skin to allow the burying of a strip in the final stage of the operation?

Mr. E. W. Riches said that he had carried out a number of operations in which he had tried to follow Johanson's technique, and with the posterior strictures it was rather complicated to make the scrotal funnel and to get it accurately opposed to the urethra. The opening tended to contract and after six weeks a very narrow orifice into the urethra was found, without necessarily stenosis of the urethra itself. Mr. Riches wondered now whether the scrotal funnel had been necessary in all these cases because if one could do without it the operation was obviously very much simpler.

The President said that in the recent past, at any rate, stricture cases were very often looked after by junior residents and perhaps did not receive individual attention. His own feeling was that a patient who had to be dilated as often as monthly, needed other treatment.

He favoured a more aggressive surgical attitude. Urethrograms were useful but sometimes a little difficult to interpret. In many cases he preferred to make a permanent perineal opening in the bulbous urethra proximal to the stricture. Such an opening was easy to keep patent, and the stay in hospital after the operation was short.

Mr. Swinney, in reply, said that Mr. Moore might well be right in that there was no need to have an inlying catheter after the first stage. However, a catheter did help to keep a rather moist area dry.

With wide undercutting of the perineal skin he had never had any difficulty in burying a strip of skin in that situation.

Seminal Tuberculosis

By Howard G. Hanley, M.D., F.R.C.S.

In the last few years genito-urinary tuberculosis has become a fruitful field for research in conservative surgery with a much more hopeful prognosis.

The primary genito-urinary lesion in most cases is in the kidney, but some people believe it can be in the prostato-vesicular region, or in the epididymis. Whichever is correct, I would stress the importance of the prostate and vesicles as a source of symptomless latent infection. Whether it is possible clinically to separate prostatic from vesicular involvement I do not know.

Semb (1953) mentions that in a group of 54 men with renal tuberculosis, the prostate was involved in 30, the vesicles in 3 and the epididymes in 11, but he does not say how he decided that only the prostate or only the vesicles were involved in some of the cases. Rectal palpation may give adequate evidence of a positive nature, but I think it is valueless as a means of excluding a lesion in either organ.

Tubercle bacilli in the seminal ejaculate fluid could come from the epididymes, the vesicles or the prostate. Where there is no clinical evidence of epididymal involvement I am assuming that the bacilli come from the vesicles or prostate or both, but I do not think it is possible to differentiate any further than this in most cases, and I have therefore called this seminal tuberculosis.

The importance of seminal tuberculosis lies in the fact that not only may it provide the earliest proof of a tuberculous infection, but it may also lie dormant for very many years in an otherwise healthy and unsuspecting patient.

Ross (1953) and Gow (1953) reported in the B.A.U.S. review that 53% of the male patients had a genital lesion of some sort, 28 being epididymal. In the Institute of Urology Mr. C. I. Murphie and I have recently carried out a review of all Ministry of Pensions cases of g.-u. tuberculosis recorded since 1940, and it is clear that 35% of the men concerned reported to their medical officer because of a swelling in the scrotum. In many instances this had been present from three to six months. The history and clinical examination revealed other lesions in keeping with the B.A.U.S. series, but it was the epididymis which convinced the man that something was wrong. A careful review of the case notes shows that over 11% of these men were diagnosed as having non-specific epididymo-orchitis and were returned to their units for some months before the correct diagnosis was established.

There is no need to be hypercritical of this fact. In the absence of any other obvious tuberculous lesion, I do not know how one diagnoses an acute tuberculous epididymitis before it either develops a sinus or settles down into a hard nodular lump. The most thorough urine examination may not reveal tubercle bacilli in these early cases, or in fact at any time if the urinary tract is not actively involved, but there is no doubt that the majority of these early acute cases will have tubercle bacilli in the ejaculate.

In recent months I have seen several such acute cases, chiefly in young National Service men. The acute stage subsided so rapidly in one man that he was returned to his unit in three weeks following a completely negative urological investigation. However, after six weeks his seminal fluid culture grew tubercle bacilli and he was promptly recalled. He still had no clinical signs. His prostate and vesicles felt normal on palpation and his epididymal thickening was certainly not diagnostic of tuberculosis. But again his ejaculate contained tubercle bacilli and he is now on a prolonged antibiotic course. Surely this is the type of case where we may hope to cure a genito-urinary lesion with sanatorium and antibiotic therapy.

Epididymo-orchitis is now such a rare complication of gonorrhœa that an epididymitis in a young man to-day is probably a coliform or a tuberculous infection. A coliform infection can produce an

abscess and a discharging sinus on occasion, but months of waiting for a clinical diagnosis may be avoided by a seminal culture. Only an ejaculate specimen is of any real value. The few drops of mucus and possibly vesicular fluid one obtains after prostatic or vesicular massage are a waste of time to culture.

My interest in this problem was stimulated by 3 patients who were seen in the subfertility clinic, with complete azoospermia.

The first man aged 33 had been married seven years, and was symptomless from a urological aspect. His wife had undergone much gynæcological interference before Dr. H. A. Davidson discovered his azoospermia. His testicles were normal but rectal examination revealed two hard fixed vesicles which were immediately diagnosed as tuberculous. His seminal fluid contained pus cells and acid-alcohol-fast bacilli in about equal proportions. He had a non-functioning calcified kidney but although his urine never at any time contained tubercle bacilli, the kidney after nephrectomy contained living bacilli which were cultured. His ejaculate remains contaminated three years later in spite of antibiotic therapy.

The other two men were also azoospermic and were referred to the clinic with pyospermia. They gave no history of any genito-urinary symptoms and, unlike the first man, had no clinical signs of vesicular involvement, but the seminal fluid gave a positive tuberculous growth. No other genito-urinary focus has been discovered so far in either patient.

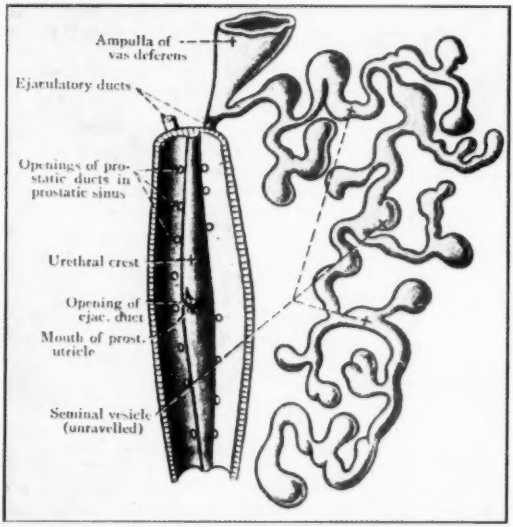

FIG. 1.—Diagram of prostatic urethra and seminal vesicle from E. B. Jamieson's "Illustrations of Regional Anatomy". By kind permission of the publishers Messrs. E. & S. Livingstone, Ltd.

Seminal tuberculosis does not necessarily cause azoospermia and 4 further cases were detected owing to the persistence of a pyospermia after adequate sulphonamide therapy. One man's sperm count was down to 30 millions per c.c. but the others were well within normal limits. No clinical signs of tuberculosis were detected in the genito-urinary tract apart from a positive semen culture, and some dubious nodularity in the prostate. I am now very suspicious of any pyospermia which does not show rapid improvement on sulphonamides, and I think this view is justified by the detection of these 7 cases of genital tuberculosis in the subfertility clinic in three years.

If we refer to Fig. 1 it is obvious that involvement of the seminal vesicle alone will have little effect on the number of sperms or even on the ejaculate volume until a large area of the vesicle is destroyed. Further vesicular destruction now results in a progressive drop in the ejaculate volume, but provided that the vas, ampulla and ejaculatory ducts are patent the sperm numbers will be unaffected.

In my experience, by the time the vesicles are palpable, the ejaculate volume has been reduced to 1 c.c. or less. One patient has had bilateral vesiculo-prostatic involvement and a unilateral epididymectomy. He produces no ejaculate whatever but live sperms are present in the first few cubic centimetres of urine passed after an orgasm. Obviously the vas, ampulla and ejaculatory duct on one side are still patent though the vesicles are destroyed or blocked.

Prostatic tuberculosis probably has little effect on the ejaculate volume or upon the sperms until obstruction of the ejaculatory ducts occurs when, of course, a total azoospermia results.

As I mentioned previously, it is very difficult and perhaps impossible to be sure that only the prostate or only the vesicle is involved. I can understand, however, that if the prostate is not infected the urine may never contain tubercle bacilli, a situation frequently found in cases of tuberculous epididymitis, but these are the cases where a seminal culture is of value, because all 5 of the acute cases I have met with have had a positive ejaculate culture. This finding must be treated with great caution, since the series is too small to be important, but obviously if we continue to find positive cultures in all the epididymitis cases even when there appears to be no clinical vesiculo-prostatic lesion, it will add great support to the theory that the epididymis is involved secondarily to the prostatic area and the condition is not a blood-borne infection.

Before leaving the question of subfertility I would point out that seminal tuberculosis of even long standing does not necessarily produce sterility. In fact it probably only rarely does. I have 4 patients who have sired children since I first knew they had seminal tuberculosis, 3 of them having had a unilateral epididymectomy. One man who is at present in hospital undergoing a prolonged antibiotic course made his wife pregnant immediately before entering hospital, only a week or so after I had found a semen specimen full of pus cells and tubercle bacilli. The fact that semen can be loaded with tubercle bacilli over a period of years does show how resistant to infection are the female cervix and vagina, since they are so very rarely involved. Tuberculous endometritis on the other hand is now known to be much more prevalent than we once thought, and although the authorities consider it to be hæmatogenous in origin, one cannot help remembering these tuberculous ejaculates.

Apart from the subfertility aspect, seminal tuberculosis is surprisingly free from symptoms or signs. We all have cases where an epididymectomy has been performed some years ago, but where the prostate or vesicles remain hard or nodular. In fact we do not often expect this nodularity to disappear even though the patient remains symptomless and his urine sterile.

In the past few months I have managed to review 7 of my old genital cases who were originally discharged from the outpatients department as cured, by an orchidectomy, and or, nephrectomy—as far as one could tell by urine examination. 4 of these 7 patients have positive semen cultures; fifteen, thirteen, eight, and five years after their last hospital treatment. All these originally had, and still have, nodular prostates so that the present activity is nothing new. One man has 3 children and another has 1 child, born since the original infection. Firm conclusions cannot be drawn from 7 cases, but it is obviously very difficult to persuade men to attend the outpatient department again after a long interval of time, particularly if they had a nephrectomy or epididymectomy fifteen years ago and now feel perfectly fit. However, where it is possible, I feel confident we shall find that if the prostato-vesicular region was originally involved, it will still be involved to-day in a high proportion of cases.

As urologists we must now decide the most important problem of whether this latent tuberculous vesiculo-prostatitis matters or not, and whether we should attempt to treat it or not. Until the advent of the antibiotics there was nothing we could do for the patients. Some more courageous amongst us, notably the late Mr. F. McG. Loughnane, advocated total removal of the vesicles, but most surgeons were content to leave well alone. Now in view of the fact that 4 out of the first 7 old epididymitis cases had active disease still present after five to fifteen years, I think we should try and treat these men. They do not necessarily remain latent for ever. For example, we have a man in St. Philip's Hospital who has just developed a tuberculous epididymitis five years after his nephrectomy. He has been symptomless all his time but he has had a latent vesiculo-prostatitis. We have all seen such cases.

If a man has a tuberculous kidney there is no question about the advisability of sanatorium regime as an adjunct to, or instead of surgery, but it is very difficult to know whether it is justifiable to urge him to have three to six months' treatment because he has a vesiculo-prostatitis.

At the moment I am urging such patients to come into hospital for three months. This period is not long enough, which makes one's responsibility even greater. Those who cannot come into hospital are being treated with a modified antibiotic course of streptomycin, isoniazid and PAS, so that in time we shall have two comparable series.

Treatment

It is too early to assess the results of antibiotic treatment in this small area of the whole large field of genito-urinary tuberculosis. My impression so far is that the seminal cultures become negative with treatment more easily than the urine from a renal lesion does, but the number of relapses after only three months' treatment is very high.

From first principles, if there is a large caseating area in the prostate or vesicles, antibiotics will not produce a cure, but we could reasonably expect good results in the absence of large areas of caseation. Some form of grading of the lesion is therefore necessary but I find this very difficult to do. The only two positive cultures which became negative after three months' treatment and have stayed negative for a year or more, had each a normal ejaculate volume, thus showing that very little of the vesicular structure had been destroyed. The majority of the other cases became negative during treatment but tended to relapse rapidly when the drugs were stopped. Six months' treatment would therefore appear to be essential in most cases, but it may well be that ambulatory treatment is sufficient if active infection is confined to the seminal system.

Conclusions

The vesiculo-prostatic system is involved in genito-urinary tuberculosis in over 50% of cases, and the seminal fluid of such cases will generally contain tubercle bacilli. These are easily cultured and this fact provides a useful adjunct to early diagnosis particularly since a clinical diagnosis may be very difficult to make.

As a method of estimating quiescence or cure of vesiculo-prostatitis the seminal culture is invaluable.

After a simple nephrectomy for a tuberculous kidney, an active but symptomless focus is left behind in the seminal tract in a high proportion of patients.

Does it matter that this active focus can be left behind and remain unsuspected for very many years? Personally I think it does matter and that we should attempt to treat the condition until it is culture negative. If this is so the days of simple nephrectomy or epididymectomy without any form of antibiotic therapy are over.

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Mr. David Band said that he was firmly convinced that the conservative treatment of genito-urinary tuberculosis in the male could be curative if the treatment was undertaken in a sanatorium, and if the patient was cared for over a prolonged period in a sanatorium with full chemotherapy. He had discussed the question of examining the seminal fluid in such patients with the physician-superintendent, but they had both felt that it was undesirable to embark on such examinations on patients already admitted to the sanatorium community.

The President said that it was well known that the death-rate in urinary tuberculosis was higher in the male than in the female.

Mr. Hanley said that he was quite prepared to admit that a long sanatorium regime was perhaps unjustified in this very chronic form of genital tuberculosis, particularly if prolonged antibiotic therapy, supervised in the outpatient department, proved adequate.

This was largely a matter for further investigation.

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Section of Dermatology

President—REGINALD T. BRAIN, M.D., F.R.C.P.

[*December* 17, 1953]

Poikiloderma with Epitheliomata.—D. S. WILKINSON, M.D.

Mrs. F. O., aged 69.

The early history of this patient is vague. She remembers having four or five patches of red skin on the shoulders and hips as a child of about 6 following some infectious fever. These apparently did not spread very much until her menopause when a rapid extension and confluence of the lesions took place. Twelve years ago she was seen by Dr. Henry MacCormac and a malignant epithelioma was removed from her left thigh. This diagnosis was confirmed histologically. She was given arsenic as a medicine for some period in her youth but for how long or for what it is impossible to discover.

I first saw her in October 1953 when she showed the same general appearance of the skin as now but had a large infiltrated lesion on the edge of the scar tissue on the left thigh and several more thick irregular crusts on the abdomen and thighs which, when removed, left a raw area and provoked some bleeding. Apart from being of a nervous disposition her health has been extremely good. There is no family history of any skin complaint.

On examination.—With the exception of her face, scalp, hands and feet, the whole of her skin shows a generalized poikilodermatous state, identical to areas of radiodermatitis in some places and in others showing a more reticulate, pigmented pattern. The skin is for the most part atrophic and lies in wrinkles and folds that can be lifted up from her chest; but in other areas, such as around the hips and thighs, it is more adherent. The general impression is one of a reticulate, scaling, slightly infiltrated dermatosis giving rise to eventual atrophy. Here and there are islands of normal or scarred skin, particularly on the arms and belly. Some of these are almost scleroderma-like in hardness. There is some atrophy behind the ears which has resulted in some shrinkage of tissue in this area. There are several areas of keratosis remaining on the lower abdomen and hips. Beneath the dressing on the left thigh is a wound from the removal of the epithelioma. This is healing very slowly. There is no generalized adenopathy, nor is the liver or spleen enlarged.

There is a kerato-acanthoma of six weeks' duration in the left cheek, which she believes arose as a result of a sting (this cannot be substantiated). It has been treated only by one application of carbon dioxide snow a fortnight ago.

Investigations.—Blood count normal. Blood W.R. and Kahn negative.

Radiography: Chest: There is sclerosis present in the left second rib anteriorly. Skull, and long bones: No bony lesion shown.

Histology: 1944: Epithelioma: "Squamous-cell carcinoma of skin; section shows invasion of dermis by fully keratinizing squamous-cell carcinoma."

11.11.53: "Section shows invasion by a keratinizing squamous-cell carcinoma. There is thickening of the adjacent epithelium with elongation of the rete pegs, some dyskeratosis and hyperkeratosis. Some of the cells have small dark shrunken nuclei and contain keratin" (H. J. Harris).

Comment.—I have been uncertain whether to regard this as idiopathic atrophy or as poikiloderma, but I think it is probably a congenital form of poikiloderma (though not that described by Thomson, 1923). Rook (1949) pointed out that there were a number of intermediate cases difficult to classify.

The epitheliomata may indeed be the result of taking arsenic; a history of this is difficult to obtain but it seems probable that she was given this many years ago. Jadassohn, however, records the occurrence of epitheliomata in poikiloderma. The histological sections almost simulate the progression of primary atrophy to a leucoplakia-like condition of epidermal thickening and an eventual epitheliomatosis that one sees in primary atrophy of the vulva but Dr. H. Haber has pointed out that the epidermis throughout shows dyskeratotic cells which Montgomery believes are indicative of arsenic poisoning.

POSTSCRIPT (25.1.54).—The kerato-acanthoma progressed to complete resolution a month after the treatment.—D. S. W.

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Werner's Syndrome.—D. S. WILKINSON, M.D.

Mrs. M. S., aged 39.

This lady has become progressively affected by her complaint in the three years that I have known her. The main symptom has been of pain in the legs leading to a considerable restriction in walking, increasing for about ten years. (Even at the age of 15 she had pains and cramps in the legs and was unable to dance or walk for long distances.) She had several attacks of thrombophlebitis during and after her pregnancies in the four years previous to the onset of this. Until two years ago she had persistent thrombophlebitic ulcers, the last of which healed two years ago. Cataracts of both eyes developed rapidly and were removed three years and two years ago. In 1951 she noticed increasing weakness of her muscles and this has persisted. There was no acute attack of muscular pain, swelling of the eyelids or symptoms suggestive of an acute dermatomyositis. There has been considerable loss of scalp hair recently and it has been turning grey. She has also had spasmodic attacks of vaso-constriction in the hands for about six years and has at times noticed difficulty in swallowing (solids rather than fluids).

In 1950 she was admitted to the Princess Beatrice Hospital for bilateral lumbar sympathectomy. Her skin temperature and pulse recordings did not show any marked improvement when taken again in 1953.

On examination.—She shows a juvenility of stature and appearance. There is some thinning and greyness of the scalp hair. She has small arms and legs for an adult of her build and a general thinness of the limbs. Apart from this the hands and arms show no particular abnormality. The changes in the skin are confined to the legs and the feet. The former show a sclerosis ("sclero-poikilodermie") rather than a scleroderma with the tightness of the skin over the toes and feet and a punctate telangiectasia with scattered pigmentation around the ankles and lower legs. The face shows pinching and tightness around the mouth and nose. The teeth are good and fingernails normal. There is considerable wasting of the leg muscles and particularly of the small muscles of the feet. There are calluses at the sites of pressure. She has a characteristic husky, high-pitched voice. General examination revealed no abnormality in other systems of the body.

Family history.—None similarly affected. No cousin marriages.

Investigations.—10.10.53: Hb 85%. E.S.R. 16 mm./1 hr. (Wintrobe). Serum calcium 10·3 mg./100 ml. Serum inorganic phosphates 2·9 mg./100 ml. Blood urea 34 mg./100 ml. Serum proteins 8·2 grammes/100 ml. (Albumin 3·15 grammes. Globulin 5·05 grammes.) Serum alkaline phosphatase 12 (KA) units.

Radiography: Barium swallow showed no abnormality. 1951: Generalized osteoporosis of bones of feet. Flakes of calcification around calcaneus. No arterial calcification seen.

Biopsy (muscle), 1951: "Section shows aggregations of apparently normal muscle fibres." 1953: "Section shows some scattered degeneration of muscle fibres."

Mr. Gavin Livingstone, F.R.C.S., kindly examined her larynx and reported:

"Both cords are moving freely. There is a slight heaping up of the epithelium in the interarytenoid space but there are no hyperkeratoses or leucoplakial areas over the cords." He concludes that he would have passed the larynx as normal in the absence of any other disease.

Electromyography: The action potentials are reduced in the tibialis anterior and, particularly, the tibialis posterior muscles.

Comment.—The diagnosis of Werner's syndrome is based on a combination of juvenile cataract and scleroderma-like changes, most prominent on the feet, but also involving the face. She shows the juvenile appearance which is described in these cases and has clinical evidence of considerable organic arterial disease in the legs. Most of her pain and symptoms, however, come from the muscle weakness and wasting which is also described in this condition.

Dermatomyositis was considered at an earlier stage but there was no sudden history of onset and although the body musculature was ill developed, there was no evidence of particular wasting at that time, except in the muscles of the feet and lower limbs.

The lack of involvement of the skin of the hands and the associated cataract are the main features that distinguish this from scleroderma.

A very similar case was shown by Dr. D. I. Williams in 1950 at this Section, and at the International Congress of Dermatology (1952). His patient, a man, also showed evidence of endarteritis, reduced action potentials of the muscles and glycosuria.

These patients suffer from a profound congenital maldevelopment of the mesodermal tissues and at the height of their adulthood they are affected prematurely by the afflictions of old age. They pass from juvenility to senescence without any intervening maturity.

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Familial Primary Self-healing Squamous Epitheliomata of the Skin (Ferguson Smith).—J. S. PEGUM, M.D., M.R.C.P.

A. B., male, aged 32. Occupation, ship's joiner.

History.—Since the age of 14 the patient has had lumps in the skin of the face, ears, hands, arms and left leg. These lumps are painful at first, and in the course of a few months they ulcerate or drop off, leaving scars behind. The patient states that a maternal aunt, his mother and his sister have had similar lesions.

When first seen in August 1953, he had pitted scars on the ears and nose, and dome-shaped umbilicated lesions on the ears, the left hand and on the left leg. The appearance of these lesions recalled that of button epithelioma (kerato-acanthoma). These lesions were treated—some by excision and some by curettage. When seen again December 1953, he had developed fresh lesions on the forehead and on the right cheek. There were small papules surmounted by a hard crust; on the left pinna there was a pearly irregular epidermal thickening, 2 cm. by 1 cm., and a crateriform ulcer 0·5 cm. in diameter. On the right pinna there was a similar ulcer.

Biopsies of the skin.—(1) Warty lesion from the forehead, removed August 1953:

There is thickening of the horny layer, with parakeratosis. The epidermis shows downward proliferation into the dermis. There is a moderate infiltrate of lymphocytes and plasma cells.

(2) A dome-shaped lesion with a central horny punctum on the left leg:

There is a central mass of horn, in part parakeratotic, surrounded on all sides but the external one by prickle-cell layer which is hypertrophic in some places, atrophic in others. In the dermis there are downgrowths of well-differentiated prickle cells with cell nests and horny cysts. There is moderate infiltration of lymphocytes and monocytes together with fibrocytic proliferation.

Comment.—This is the condition described by Ferguson Smith (1934). Some of the lesions presented in the past by this patient have borne a striking similarity, both clinically and histologically, to molluscum sebaceum (kerato-acanthoma). It has been suggested by Whittle and Lyell (1952) at this Section and by Fouracres and Whittick (1953) elsewhere that the Ferguson Smith type epithelioma and molluscum sebaceum are the same condition.

Until this patient came under our care he had had no treatment but had allowed his lesions to heal spontaneously. Now, having had some epitheliomata excised, he has become a convert to treatment since the scars left by excision are much less obvious than those produced by the process of spontaneous healing.

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Dr. J. Ferguson Smith: The condition in this case is identical with the one I originally described. We have a good many such cases now in the West of Scotland and we find quite a number occur in families. Two cases have been recorded, one fairly recently, from the United States (Witten, V. H., and Zak, G., 1952, *Cancer*, **5**, 539). Another in the United States has been mentioned though I do not think it has been published and the number is growing.

The deep penetration of some of the lesions is astonishing. We have sections showing deep epithelial infiltrations of lymphatics, in the ear, for example. If a sufficient number of sections are studied other abnormalities will be found and one gets all the criteria of malignancy, though in small amounts. At the time I published my paper, in 1934, the distinguished pathologists to whom I showed the section had no reservations at all about accepting the evidence as to early malignancy. It is only because all these cases have since been reported and the patients have not died nor shown other signs of malignancy that the opinion has grown up that after all they may not be malignant. Most of these cases start early in life. In the family which I first described the disease in the daughter started at the age of 15. Whether the condition is malignant or not is a matter of opinion but it is a distinctive disease.

The President: In this case I discovered that the patient was a carpenter who used a lot of pitch and tar in building boats. Other cases have occurred among Clyde workers who use pitch and tar. On the other hand I have no doubt that in Dr. Ferguson Smith's youngest case, aged 15, it would be considered idiopathic.

Dr. Ferguson Smith: One case occurred in a man who had only recently started working in a coal mine but another occurred in a woman who was engaged in household duties. In at least one of the American cases there might have been an association with tar and shale. In tar epitheliomatosis one usually gets a pre-epitheliomatous condition, but in these cases one starts with a fairly normal skin and finds the appearance diagnosable from the beginning. These lesions are not secondary to anything else. As I pointed out in my first account, it is the "young" and healthy condition of the skin round about the lesion which is very significant.

Dr. Hugh Gordon: It is not always necessary for tar warts to occur on the so-called shagreen skin. At the Royal Cancer Hospital we frequently see small tumours, so-called tar warts, which in our opinion are often early molluscum sebaceum, occurring on quite healthy skin in tar workers.

The following cases were also shown:

Lamellar Desquamation of the Newborn (Fœtal Ichthyosis).—Dr. J. E. M. WIGLEY.

Acridines in the Treatment of Mycosis Fungoides.—Dr. C. H. WHITTLE and Dr. J. L. MOFFATT.

Kerato-Acanthoma of Right Ear.—Dr. J. L. MOFFATT and Dr. C. H. WHITTLE.

Dermatitis Artefacta.—Dr. R. D. SWEET.

Lupus Erythematosus with Unusual Buccal Lesion: Loeffler's Syndrome after Mepacrine.—Dr. D. S. WILKINSON.

Discoid Lupus Erythematosus. Mepacrine Sensitivity.—Dr. P. A. J. SMITH (for Dr. W. N. GOLDSMITH).

Keloids and Acromegaly.—Dr. P. J. HARE.

Porokeratosis of Mibelli.—Dr. R. G. HOWELL (for Dr. E. W. PROSSER THOMAS).

Argyria.—Dr. R. G. HOWELL (for Dr. G. B. DOWLING).

Scleredema Adultorum of Buschke.—Dr. D. L. REES.

Scleredema Adultorum of Buschke.—Dr. K. D. CROW.

Late Lues.—Dr. N. A. THORNE.

(These cases may be published later in the *British Journal of Dermatology*.)

[*January* 21, 1954]

Exfoliative Dermatitis with Lymphatic Leukæmia.—J. FIELDING, M.R.C.P., D.P.H., and H. T. H. WILSON, M.R.C.P.

Dr. WILSON:

The patient is a widow, aged 64. Four months ago the backs of her hands began to itch. After a few days a rash developed and spread to the arms, face, scalp and trunk. Originally patchy, in a few weeks it became universal and has remained so. Her general health has remained good. She had scarlet fever in childhood. She has had eczema of the face, chest and arms off and on since infancy but never previously universal. Epileptic, but no fits for many years. Her mother died at age 27. Her father died at 57 (cerebral tumour). There are no siblings. The patient has two children alive and well.

On examination generalized exfoliative dermatitis was found with profuse scaling, particularly over the legs; skin comparatively pale elsewhere; diffuse hair loss with some regrowth; dystrophy of all nails; tongue smooth; moderate universal lymphadenopathy. No abnormality was found on general examination. Liver and spleen not palpable. Blood count (September 22, 1953): R.B.C. 3,420,000; Hb 7·25 grammes % (49%); C.I. 0·7; W.B.C. 55,000, neutrophils 8, eosinophils 9, lymphocytes 29, lymphoblasts 2, smear cells 51%; 1 nucleated red cell. Sternal marrow (October 1, 1953): a cellular marrow showing lymphatic leukæmia. Serum proteins (January 18, 1954): total protein 5·0 grammes %, albumin 2·9 grammes %, globulin 2·1 grammes %, A/G ratio 1·4/1.

Skin biopsy shows a general thinning of the prickle-cell layer although some interpapillary processes are enlarged. There is a marked dyskeratosis with a very thin layer of keratin. In the dermis the capillaries are engorged and there are patches of sub-epithelial and perivascular infiltrate, mainly of lymphocytic type with macrophages and an excess of melanophores.

Lymph gland biopsy (cervical gland).—Almost complete loss of normal architecture, gland being filled by a solid mass of small lymphocytes.

Discussion.—Although it is well known that exfoliative dermatitis may be associated with lymphatic leukæmia, I believe that these cases are very rare. Montgomery (1933) found 18 examples of various reticuloses among 73 cases of exfoliative dermatitis. In a series of 50 patients with this disorder I found only 4 reticuloses including one leukæmia.

REFERENCE

MONTGOMERY, H. (1933) *Arch. Derm. Syph., Chicago*, **27**, 253.

Sézary's Erythrodermia.—J. FIELDING, M.R.C.P., D.P.H., and H. T. H. WILSON, M.R.C.P.

Dr. WILSON:

Widow, aged 84. Six years ago she developed a generalized itching and scaling rash which has persisted ever since. In May 1951 she was admitted to Paddington Hospital for an injury complicating an osteo-arthritis of the spine. In August 1951 she was readmitted after a cerebral thrombosis and remained in hospital for six weeks. During this time the skin remained unchanged. In 1953 the rash became more severe. There has been no change in the condition since then. Her general health has remained good and her appetite is keen.

She gave a history of hysterectomy and oophorectomy for menorrhagia forty years ago. The family history was that the father died aged 43, of pulmonary tuberculosis; the mother died aged 53 of heart trouble; 4 brothers and 2 sisters died of tuberculosis; 1 sister died of heart disease and 2 children are alive and well. On examination the skin was red, scaling and pigmented. There was slight dystrophy

of finger and toenails and gross generalized lymphadenopathy. There was left facial weakness. She was edentulous. The tongue red and smooth. Chest normal. B.P. 195/105. Liver and spleen not palpable.

Discussion.—The presence of giant mononuclear cells has been reported in blood films from 5 previous cases of exfoliative dermatitis (Baccaredda, 1939; Sézary, 1949; Wilson and Fielding, 1953). Some of these patients have had mucosal involvement, gross œdema of the face and abdominal wall and hepato- and splenomegaly. These clinical features have not been constant and there is insufficient evidence to regard the condition as a reticulosis or even a separate clinical entity. Many more cases of exfoliative dermatitis will have to be examined before we can say whether the mononuclear cells are common or not.

Dr. FIELDING:

In the peripheral blood this case shows a high proportion of mononuclear cells with characters distinguishing them from the known blood cells and their precursors. We have now seen 2 cases with similar appearances. The peripheral blood shows a constant mild anæmia Hb 60–70%; R.B.C. 3 to 4 million per c.mm.; no nucleated red cells have been seen at any time; W.B.C. have varied between 12,000 and 22,000 per c.mm. The absolute number of polymorphs is in the normal range; the leucocytosis is due to many atypical mononuclear cells in the peripheral blood. Sternal marrow puncture reveals no definite infiltration; skin biopsy shows a sharply defined infiltration of the corium with large mononuclear cells similar to those in the peripheral blood; biopsy of a superficial lymph gland has shown the non-specific changes of so-called lipomelanic reticulosis. There is, at present, no evidence of infiltration affecting any organ other than the skin.

This new cell type assumes two main forms with all intermediate forms between. The first form, which predominated in our previously reported case, is a very large irregular cell 40–50 μ in diameter. The cytoplasm is tenuous, vacuolated with irregular pseudopodial processes and resembles a histiocytic reticulum cell. The nucleus is rounded and convoluted in a characteristic way, sometimes showing indistinct nucleoli. The second form, which predominates in the present case, is rounded and smaller, about 15–25 μ in diameter, with a hazy and vacuolated cytoplasm and the same convoluted nucleus. It bears a superficial resemblance to the lymphocyte series. This second form was described by Sézary. Many binucleated cells of this type are seen and an occasional mitosis has been observed in the peripheral blood.

In our first case of this condition these cells were few in number at most examinations, about 1% to 2% of the nucleated cells, but we saw two episodes in which showers of cells entered the blood stream and the proportion of abnormals rose to 17% to 20%. This intermittent flooding of the peripheral blood is also mentioned by Sézary. At every examination in the present case these cells have accounted for 50% or more of the nucleated cells.

We believe that this type of case is probably common amongst exfoliatives and requires further study including post-mortem examination.

We are indebted to Dr. J. E. M. Wigley for permission to present these cases.

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Dr. J. E. M. Wigley: On the case labelled Sézary's erythrodermia Dr. Wilson does not think that these cases are recognizable clinically. I would say that one may have a shrewd suspicion, if not a certainty, from the clinical appearances. Sequeira and Panton (1921) originally described as lymphoblastic erythrodermia cases characterized by a peculiar reddening and thickening of the skin, accompanied by lymphadenopathy and generalized intense irritation. The peculiar colour I can only describe as that of old well-weathered brick seen in the waning autumn sunlight. Are the cases described by Sequeira and Panton of the same nature as that of Sézary's erythrodermia? Clinically they look identical.

REFERENCE

SEQUEIRA, J. H., and PANTON, P. N. (1921) *Brit. J. Derm.*, **33**, 391.

Arsenical Keratoses and Epithelioma with Bronchial Carcinoma.—C. D. CALNAN, M.R.C.P.

H. B., man aged 59.

History.—He had psoriasis at intervals since childhood. Treatment with Fowler's solution was given over several years. For twenty years at least he had noticed warty lesions on his hands and feet and for two years a persistent ulcer over his lower back.

Examination (April 1953).—A few signs of psoriasis on his elbows. Profuse arsenical keratoses on the palms and soles and the backs of the hands. Basal-cell epithelioma over lumbar area.

Histology.—Tumour of back is a basal-cell epithelioma. Keratosis on back of hand is a keratoma with Bowen changes.

Progress.—August 1953: Developed carcinoma of right lung for which he had a pneumonectomy. November 1953: Pleural effusion which contained malignant cells. Died suddenly 21.11.53.

Comment.—There is still considerable discussion among physicians as to whether arsenic can cause cancer of the lung. Neubauer (1947) found only 2 cases of lung cancer among 143 patients following prolonged arsenic medication. Recently Sommers and McManus (1953) have published an account of multiple arsenical cancers of internal organs.

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SOMMERS, S. C., and MCMANUS, R. G. (1953) *Cancer*, **6**, 347.

Dr. Louis Forman: I recall two cases of malignant disease of the lung with multiple basal-cell epithelioma. There was no history of the ingestion of arsenic in both cases. However, one knows that arsenic is responsible for multiple epithelioma of the skin. In the article by Sommers, mentioned by Dr. Calnan, there are examples of carcinoma of the œsophagus, bladder, prostate and breast associated with carcinoma of various types of the skin, following the ingestion of arsenic.

The following cases were also shown:

(1) Xanthomatosis. (2) Trichophyton Rubrum Infection.—Dr. R. M. B. MACKENNA and Dr. C. D. CALNAN.

Case for Diagnosis. ? Chronic Lymphatic Obstruction Following Injury.—Dr. BETHEL SOLOMONS, Jr.

(1) Cutaneous Leishmaniasis. (2) Acne Agminata.—Dr. R. H. MEARA.

Premycosis.—Dr. STEPHEN GOLD.

(These cases may be published later in the *British Journal of Dermatology*.)

Section of Anæsthetics

President—Professor R. R. MACINTOSH, M.A., D.M., F.R.C.S.Ed., F.F.A.R.C.S., D.A.

[*December* 4, 1953]

Antihistamines in Anæsthesia

By A. J. W. BEARD, M.D., D.A.

My own interest in the antihistamine drugs in anæsthesia goes back some two years, and was aroused, in the first place, by Phenergan and its derivative Avomine in the prevention of car sickness, and its very welcome sedative effects on my own children on long journeys.

The antihistamine drugs are not a homogenous group, but are of widely differing chemical constitution falling roughly into four groups, many having sedative and anti-emetic properties which may be of use to anæsthetists. Phenergan shows these effects and is the drug with which I have most experience. Recently closely related phenothiazine compounds have been synthesized in France and chlorpromazine (or Largactil) has been used on the Continent for a variety of purposes. This latter drug has but weak antihistaminic properties compared with some others but these have been demonstrated sufficiently strongly, both in England and America, to justify including chlorpromazine under the abbreviated title of "antihistamines in anæsthesia".

It is known that antihistamines have multiple pharmacological properties some of which resemble those of procaine, some of atropine, of pethidine and of quinidine and it has been shown (Dutta, 1949) conversely, that these drugs in their turn also have some antihistaminic properties. In fact all of them, antihistamines included, inhibit acetylcholine, adrenaline and histamine in varying degrees (Burn and Dutta, 1948).

The various effects claimed for these drugs are rather more than adequately set out in the Continental literature; while the animal work has been largely confirmed both in England and America. I would like to mention briefly some of these effects and discuss their value in anæsthesia.

Sedation.—In the case of some antihistamines, especially Benadryl, Phenergan and its derivative Largactil, this is marked in most but not all patients. There is often some euphoria, rarely excitement is seen and is said to be most likely to occur soon after the giving of a large dose before the sedation sets in: animals develop convulsions after very large doses.

This sedation seems to differ from that of barbiturates as is shown by the behaviour of rats conditioned by an electrical stimulus to climb a pole when a bell rings. After a barbiturate, the rats stop climbing when they become drowsy, but after these drugs, especially chlorpromazine, they stop climbing when the bell rings before they become sleepy clinically, although they may still respond to the primary electrical stimulus.

In man, using the flicker fusion photometer, an instrument which shows an intermittent light, this seems to become continuous when drowsiness occurs from a barbiturate, but it becomes a continuous light earlier and before the onset of drowsiness in the case of antihistamine administration (Roback, Krasno and Ivy, 1952).

These findings suggest a difference in the effects on the brain produced by antihistamines and by barbiturates. The electro-encephalogram shows sleep patterns with chlorpromazine as distinct from the patterns seen with barbiturates. There is too, I think, some evidence of this difference derived from the experience of psychiatrists who use chlorpromazine. They find that while initial large doses quiet many excited patients and induce sleep, this sleep effect diminishes and after a few days patients can sit about while taking doses which rendered them almost comatose earlier on. In the favourable cases excitement and confusion may remain controlled in ambulant patients as long as the drug is continued, though perhaps in reduced doses, but when it is stopped many cases relapse (Stevens, 1953).

There seems to be a disinterestedness and a detachment in these patients, some of whom may still experience their hallucinations but are no longer disturbed by them.

The term "a chemical leucotomy" has been used and it will be remembered that the operation of leucotomy has been performed for pain in incurable disease. The patients are then said to experience

their pain but it no longer worries them. Similarly chlorpromazine has no analgesic effect of its own—but good results have been reported in such cases as post-herpetic neuralgias and the effects have been described as an indifference to, rather than an absence of, pain (Sigwald and Bouttier, 1953).

Anti-emetic properties.—The value of drugs in post-operative vomiting is difficult to assess; in the first place vomiting is not common nowadays after anæsthesia, and may be due to several different factors of which the psychological factors are perhaps the most difficult to evaluate but it seems unlikely that the enthusiasms or otherwise of the medical and nursing staff are without their effect on patients. Series of cases have often been too small to determine the drug effects on a symptom which may result from several causes. Perhaps the most helpful results come from the study of patients in whom vomiting is common, such as for example after fenestration operations, or thoracoplasty under local anæsthesia, and it would be interesting to see the results of these drugs in those who have a history of repeated vomiting after ordinary anæsthesias. It is in these two groups of cases together with such non-surgical conditions as the vomiting of pregnancy, uræmia, irradiation and drug sickness that I believe phenothiazine derivatives will give a useful but not complete protection from vomiting.

When hypnotic or anæsthetic drugs are given to animals treated with antihistaminics sleep time is prolonged (Winter, 1948). This effect, which also occurs in man, has been called "potentiation". This term used in homœopathy implies increased power with increasing dilution and this is not accepted in scientific circles. In pharmacology if it means anything it would imply more than the mere summation of the effects of the two agents.

Hypothermia

The body temperature is maintained constant mainly by the vasoconstriction or dilatation of the skin vessels and by the heat produced by muscular activity which may range from invisible to visible as shown by shivering. This muscular activity when increased results in increased oxygen consumption which is seen experimentally in unanæsthetized animals exposed to cold. Deep anæsthesia or curarization prevents muscular activity. In these cases if the body is exposed the temperature will fall.

It will be seen that chlorpromazine is effective in much smaller dose than the other two agents (Fig. 1) (Courvoisier *et al.*, 1953).

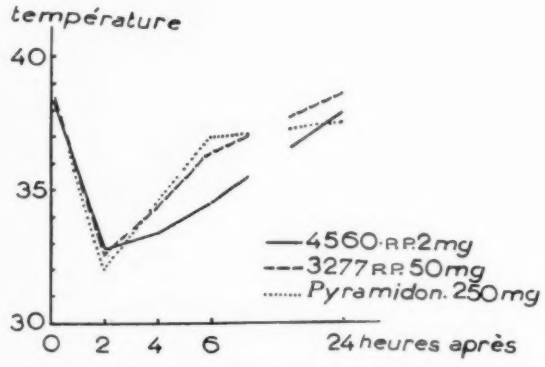

Fig. 1.—Comparative effect of 4.560 R.P. (chlorpromazine) with that of promethazine and of amidopyrine on the rectal temperature of mice (Doses mg./kg. subcutaneously). From *Arch. int. Pharmacodyn.*, **92**, 340. By permission.

Chlorpromazine has been claimed, apart from any cooling, to reduce the oxygen consumption of brain slices *in vitro* and of the entire experimental animal. But so do most other anæsthetic agents.

Chlorpromazine administration is one, but only one, of the ways in which the body may be allowed to cool and the oxygen consumption be reduced. Another way is general anæsthesia, provided the body is exposed. Chlorpromazine may in some circumstances be a convenient method but it is not magic, though its glamour can be considerably enhanced by referring to its use as "artificial hibernation". Another bad term—in fact the literature of these drugs is bedevilled with unfortunate nomenclature.

In addition to the sedative, anti-emetic and hypothermic properties of these drugs there are also anti-hæmorrhagic and anti-traumatic shock effects which have been worked out on animals using the techniques of Wiggers and of Collip and Noble respectively. It is of interest that Wiggers *et al.* in 1948 showed that in hæmorrhage, in addition to the arterial hypotension, superimposed vasoconstriction of sympathogenic origin was a factor in making the shock irreversible and that

dibenamine, an adrenergic blocking agent, inhibited this vasoconstriction and lessened the incidence of irreversible shock. Incidentally Wiggers *et al.*, in 1945, have shown that anæsthesia with a barbiturate has also reduced the mortality from hæmorrhage.

Many other such properties, as might be expected of a member of a procaine-pethidine-atropine-quinidine-antihistaminic group of drugs, have been described.

Applications.—Its use in psychiatry, in vomiting and in severe pain, has been already mentioned. Dr. Law has seen Lacomme in Paris using chlorpromazine (Largactil) 50 mg. with pethidine 100 mg. in 500 c.c. of saline as an intravenous drip for obstetrics with satisfactory sedation and amnesia. Dr. David Morris has told me of its use in premature and neonatal babies. Infants and older children with acute infections have benefited by the cooling associated with its use. Finally the control of hyperthermic crises resulting from various causes especially intracranial, both medical and surgical, may be helped by chlorpromazine.

Surgery.—First simple premedication with Phenergan 50 mg. and pethidine 100 mg. has given reasonably satisfactory sedation and sufficient drying of oro-pharyngeal secretions for adult cases using barbiturates, relaxant and nitrous oxide sequence. Respiration has been rather deeper and there have been rather quieter bronchial reflexes and less bronchospasm than I would have expected from the amount of endobronchial instrumentation employed. This less depressing combination is preferable to Omnopon and scopolamine in such cases as bronchitis with spasm and secretions, and also in cases where vomiting has occurred after previous operations. I would mention, however, that Omnopon with scopolamine costs less than 2d. for rather more sedation than is provided by over a shilling's-worth at present prices of newer drugs. The number of cases has been rather small but as yet it does not seem that the superiority of the new combination is such as to justify its use except in special cases.

This premedication followed by the intravenous administration of Phenergan 50 mg., pethidine 100 mg. and Largactil 50 mg. (the so-called "lytic cocktail") given over a period of some thirty to sixty minutes induces a twilight state in which there is, in most cases, a fall in blood pressure to about 80 mm.Hg. This fall may be increased by posture, though not very markedly, by intravenous procaine or by further blocking agents. In my cases the pulse has often been rather rapid.

I have used this method of sedation for thoracoplasties under local anæsthesia and it is, I think, the most satisfactory that I have yet tried. For general anæsthesia, using nitrous oxide-oxygen mixtures, reduced amounts of thiopentone are needed. There is often a useful degree of hypotension, the bronchial reflexes are less active while the respiration seems to be less depressed than with some other sequences.

After operation, in successful cases the patients are pale, lying quiet with eyes closed apparently untroubled by pain, but capable of responding to requests to move or to cough. The pressure tends to remain low while the drugs are active and pain when it comes on some hours after an operation may be resented by a patient who has hitherto been comfortable. Relative content may be restored by pethidine or occasionally a further dose of chlorpromazine given intramuscularly. So far the method is not unduly complicated and is, with variations, widely employed by Continental anæsthetists who do not necessarily accept all the hypotheses and theories which are advanced in support of the full technique of "artificial hibernation"; and who would regard the practice as having become unduly complicated and carried further than is justified.

The protagonists of the method, to use their own terms, say that in "severe aggressions" it is necessary to produce a "vegetative disconnexion" by continuing these drugs for up to three or four days after operation. During this period careful supervision is needed, increasing the demands on nursing and medical staff. Metabolism is supported by a variety of drugs. Afterwards the patient is gradually "liberated" from his hibernation, being allowed to rewarm.

The newer variations, which may or may not prove more useful, now employed on the Continent for so-called "potentiated anæsthesia", include Regitine (Ciba) with Antistine (Huguenard), Hydergine with antihistaminics (Kern) and Pendiomid (Ciba) with Phenergan (Ciocatto of Turin and Holmann of Berlin).

The common factor in all the combinations seems to be a sympathetic blocking agent together with an antihistaminic: the latter presumably mainly used for its sedative properties. The Continental use of the word "ganglioplegic" as applied to say chlorpromazine does not mean what we mean by a ganglion-blocking agent such as hexamethonium but corresponds more closely to the term "arti-adrenaline" or "sympathetic blocking" effect.

We are not justified in dismissing these combinations of agents because we do not care for the terms in which they are described. They are apparently proving satisfactory to very large numbers of Continental anæsthetists possibly owing in part to two factors: firstly the power of some of these drugs to produce anti-hæmorrhagic and anti-traumatic shock effects, and, secondly, to the central sedative and anti-emetic action which provides smooth anæsthesia: thus lessening the demands on blood banks and anæsthetic skill, both of which are in some places in relatively short supply. While uncritical enthusiasm is unreasonable, so is condemnation without either trying the drugs or reading the literature. Personally I would be sorry to be without the help of these drugs in certain cases.

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Observations on Hypothermia

By ANDRÉ A. JUVENELLE, M.D.(Paris)

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IT should be clear at the start that my experience with cold in biology has been mainly experimental. In fact I started to apply cold to humans with my Chief and friend Doctor Olivier Monod only recently. As the phenomena observed above 25–20° C. are strikingly different from those observed below the 20° C. range, I would suggest the following definitions in this new field of cold therapy (*see* Juvenelle *et al.*, 1952; Juvenelle, 1952):

Hypothermia: Cooling of the whole body down to a temperature of 25° C. regardless of the means used to attain this cooling.

Deep Hypothermia: Cooling of the whole body from 25° C. downwards.

Hibernation: A normal biological winter sleep in certain species.

Artificial hibernation: The induction of hibernation in the hibernating animal at a time when it would not spontaneously go into hibernation (N.B.—There should be no such thing as artificial hibernation during summer, since hibernation, etymologically speaking, means winter sleep).

Refrigeration: The cooling of a part of the body.

In its modern aspect of therapy the pioneering has been done by men like Allen, Smith, Fay, Talbott and Templeton almost fifteen years ago. More recently, Bigelow applied the biological properties of cold to cardiac surgical problems. Laborit developed a method of anæsthesia for which great advantages are claimed; this method he and his co-workers named "artificial hibernation," after Simpson. Today almost anything that puts a patient to sleep is called artificial hibernation, so that little by little another irrational, emotional and almost pre-logical concept is being introduced in Medicine.

I do not believe that the so-called ganglioplegic drugs are of use in the low temperature range; indeed I believe they are dangerous then. These drugs cannot, in themselves, reduce metabolism to a much lower degree than other drugs like ether. Cold, as we need it in various types of surgery, should be resorted to to reduce metabolism to a very low level and drugs are to be considered with extreme caution in this respect. We want to be able to work into the heart cavities, we want to be able to close the aorta above the renal arteries for a prolonged period, we want to offer the critically ill patient a satisfactory relief when oxygen is badly needed, we want to utilize a reduced artificial heart-lung system; we look to cold to meet these requirements.

It may be possible that some day we will be given another wonder drug, a drug which would arrest life for a predetermined length of time, or at will would decrease its metabolic rate. But it is my belief that until this Rip Van Winkle-making agent is discovered, cold is the best agent we know capable of reducing tissue metabolism at will.

(*a*) In order to induce cooling in a non-hibernating animal it is necessary to prevent shivering and to annihilate consciousness. Any anæsthetic that can prevent shivering can be used. However, the ideal non-toxic agent has not yet appeared.

(*b*) Consciousness may be obliterated by anæsthesia. Shivering may also be prevented in a number of ways, even by means of Largactil, Phenergan and curare, but I prefer to use the simplest way: ether.

(*c*) In other words there is not the smallest difficulty due to the induction of cooling. However, the effects of shivering-blocking agents may be entirely different at low body temperatures, and one of the major problems in this field of hypothermia is the utilization of the least toxic, rapidly eliminated agent or combination of agents.

Barbiturates are poorly eliminated by the cold animal, and the colder the temperature the slower the elimination, there even seems to be a summation of repeated injections of the drug during cooling.

In the 20° C. range no further anæsthesia seems necessary. Respiration stops around 26–30° C. under Nembutal anæsthesia, it stops around 17–15° C. under ether. The better results observed under

ether as far as ventricular fibrillation is concerned are probably related to a better ventilation under ether with better CO_2 elimination and consequently more adequate blood pH.

Considerable biochemical changes are observed in the blood during hypothermia. It is obvious that these changes may be of very little significance since we do not know what happens in the cells themselves. I daresay, however, they are not very deleterious biologically in view of the fact that they are reversible.

It is known that if pre-cooling anæsthesia is satisfactory, the oxygen consumption is reduced parallel to the drop in rectal temperature. And since it has been possible in many of my own dogs to get them back to normal behaviour after reduction in body temperature as low as 12° C., there are some reasons to believe that the O_2 uptake is, within limits, a valuable indicator of tissue metabolism. I cannot ascertain, however, whether an oxygen debt has not been accumulated during the cooling period to be paid back during the rewarming period. Should this be the case, important organs are certainly capable of removing O_2 without any debt: the brain tissue cannot accumulate such a debt, nor can the medulla, and the heart is not able to stand it any longer.

Therefore, I am driven to the conclusion that cold, in itself, does not prevent the tissues getting oxygen from the blood. It is important in this respect to remember that the heart has been shown capable of removing oxygen in a normal way at 17° C. with a partial pressure of O_2 of no more than 17 mm.Hg. On the other hand it is known that cold produces a leftward shift of the Hb dissociation curve; accordingly it has been claimed that the tissues could not remove enough for their need. This has been disproved although not entirely. When ventricular fibrillation appears, we have been able to maintain this condition during a mean period of two and a half hours by means of an artificial circulation, and get 6 animals out of 14 alive after rewarming from temperatures ranging from 12 to 20° C. (cf. "A new method of extra-corporeal circulation", Juvenelle, Lind and Wegelius, 1954). The minute blood flows used to support the entire animal were ten to twenty times lower than they should have been at normal temperature. ECGs taken during these experiments may be consulted in the paper referred to.

It has also been shown that under ventricular fibrillation the heart oxygen uptake is equivalent to what it is during normal work. Ventricular fibrillation is an expenditure of energy, and it remains to be seen if this expenditure can compare to the normal work during normal beating at any temperature. I believe, with no definite proof, that it can, provided the coronary circulation is supplied with fully oxygenated blood during fibrillation. Should this prove true, the experiment just referred to would prove that the ability to secure a good oxygen supply to the cold tissue is not curtailed by an intrinsic inability of these tissues to remove oxygen.

In any case, in a large number of dogs cooled to a mean temperature of 16° C., all fibrillating under an artificial circulation, during more than a mean period of two and a half hours we have always been able to get the heart back to normal beating. We had three failures, and all three were satisfactorily explained. This is so clear to me that I will venture to repeat that:

> When the heart starts to fibrillate (ventricular fibrillation), it is ALWAYS feasible to return it to normal beating, provided the coronary circulation has been properly maintained during fibrillation, with adequate oxygen supply to the arterial blood.

It may be worth noting in this respect that in one case the artificial circulation supporting the entire animal (which was not breathing) lasted for seven hours and the ventricular fibrillation for five hours. The temperature was 12° C. for many hours. The dog did very well after rewarming. After a few days the ECG and the EEG were identical to pre-hypothermia controls on the same dog.

Blood pressure maintains a good level down to about 25° C., then it starts to get lower. Incidentally I have found, quite empirically, that the B.P. of dogs given antihistaminics prior to hypothermia keeps at a much higher level than in dogs not so prepared. Since an adequate B.P. seems to offer advantages in the low temperature range, I give my dogs antihistaminics. I have no explanations to offer for this action of antihistaminics. Below 25° C. the B.P. starts to decrease and may reach very low levels. If anæsthesia is adequate and prevents shivering the pulse will start its fall parallel to the temperature fall.

From the biochemical angle we (Juvenelle *et al.*, 1953) have found many changes. These changes are remarkably comparable to the changes that are observed in the hibernating animal. Moreover they are reversible to normal on rewarming.

Many people will ask: Has cold no dangers, is it as safe as you say?

It seems to be so in the hibernating animal in which the rectal temperature may almost reach freezing point. In the ordinary mammal, ventricular fibrillation occurs at about 16–18° C. I consider in fact that it is of fundamental importance for scientific as well as ethical reasons to emphasize differences rather than similarities. From this we shall note that in the hibernating animal all normal neurological automatic systems are maintained efficiently whatever the rectal temperature. More precisely, respiration and heart beat persist adequately for many months at central temperatures as low as 3–5° C. In the non-hibernating mammal the heart fails around 20° C. Respiration stops at the same temperature under ether or nitrous oxide anæsthesia, with barbiturates it stops much earlier.

In hibernators, the isolated nerve transmits impulses down to freezing point, in the ordinary mammal the isolated nerve is blocked about 6–8° C.; in my opinion, these are the fundamental

differences. Until they are cleared up, we must act with caution in the low temperature range. I think that heart failure in cold is the expression of a combined cardiac conduction and excitation breakdown plus a metabolic interference with normal processes (polarization and depolarization of membranes).

To be able to reach the very low temperature range without any artificial circulation even for brief periods of time we need much more knowledge.

Summary

In our estimate, cold has no seriously deleterious after-effects, when the temperature has not gone lower than 25–20° C. (this 5° difference expresses presumable differences in techniques of cooling including anæsthesia), the same holds true for man as for dogs. Our ultimate objective could be to imitate the hibernating animal both as far as the degree and the length of cooling are concerned, but at present we cannot compare an animal which can stand a few hours or a few days at 25° C. or, as in Laborit's method, at 32–35° C., to another which normally stays for months every year at 3 to 5°. This is one reason why I reject the term Artificial Hibernation. It is absurd to compare a man "artificially hibernated", because he is suffering from let us say peritonitis, to another animal which is hibernating naturally (and has been doing so for thousands of centuries) and which is in perfect health.

What is the present position of hypothermia?

In order to give the patient a fair chance, I started by postulating that until we know more, we must consider hypothermia as an insult of an unknown degree and possibly an important one in the severely ill patient.

Indications are then easier to discuss, at least at the outset of a new method: It is by balancing the surgical risk against the risk with the adjunction of hypothermia that we may hope to select the proper candidates for this type of treatment without undue accidents.

Only the experience of many will permit us to get a better appreciation of the risks involved and perfection of the method. There is a need for close co-operation between many workers in this field.

To-day as we are still at an experimental stage I can only describe the policy that Doctor Olivier Monod and myself have tentatively adopted. Cold seems to us to be of use whenever it is imperative to lower metabolism considerably without undue danger and with possible and rapid reversal to normal, and with good control over the biological variables as well.

It also appears to be valuable whenever the surgical risk *per se* would seem to be far too great without it. (Surgical shock has almost disappeared from the large centres in the U.S.A. and in many places in Europe, but it is still a drawback in many other places.)

From these requirements it can be seen that we consider the use of the so-called "ganglioplegic" drugs as useless in conjunction with hypothermia and possibly dangerous, at least in the way they are now handled. We also believe that:

(*a*) Cold (centrally) should be of a sufficient level to meet the requirements (23–26° C.).

(*b*) Pre-hypothermia anæsthesia should be accomplished with the least possible drugs. Ether is satisfactory until we get a better agent.

(*c*) Patients with low cardiac reserve should be cooled with great caution.

(*d*) Patients with low respiratory reserves should be cooled with even greater caution and adequate means of artificial respiration with a closed chest (blow and suck system).

Suitable subjects are at the present time:

(*a*) Infants with congenital cardiac defects in which operation carries a very high mortality (over 25%) due to anoxia during or after operation. In these babies we now maintain a temperature of around 30° C. during pre-operative days (until 2–3 months, blue babies do not need drugs for this; they do not shiver and their temperature drops by simply removing part of their clothes). We operate upon these infants in the 20° C. range.

(*b*) Adults with respiratory insufficiency, upon whom a thoracic operation (pulmonary) is desirable but prohibited because of fear of oxygen lack. Doctor Monod and myself have operated on several of these cases at a temperature of 23–26° C. Our general impression is favourable, but we cannot yet seriously assess the value of the method on such a small group of cases.

(*c*) Adults or very old people in whom operation carries a very high mortality rate, with the hope of reducing the surgical insult.

(*d*) Artificial circulation with heart/lung system: This I believe will be one of the major indications of hypothermia. We recommended the use of this combined procedure in 1951, and since that time we have shown that it was feasible. The main advantages we have described elsewhere.

It is imperative to have a precise definition to our meaning if we are to gain experience from each other. The phenomenona encountered in hypothermia are so strikingly different according to thermal

levels and/or to pre-hypothermia anæsthesia that we cannot be satisfied to read in an account that "an artificial hibernation" has been induced. We certainly need more precision than that, both in thinking and in ways of expression. I suggest in closing that an international agreement be reached on definitions in this field.

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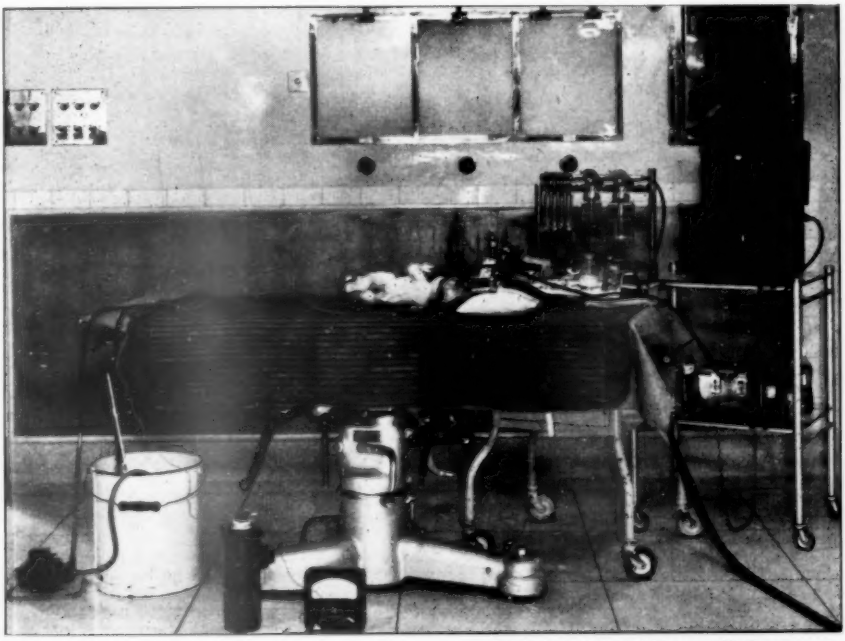
Dr. C. F. Scurr: One patient aged 76 to whom I gave 100 mg. of Largactil during an œsophagectomy dropped in temperature to 84° F. (29° C.) without any artificial cooling other than exposure to room temperature. In addition to a number of cases in which we used Largactil we have, however, had at Westminster three successful hypothermic anæsthesias in children for the performance of Blalock's operation for Fallot's tetralogy. In these no special drugs were used.

The set-up is shown in Fig. 1 and the various items are as seen. The child is anæsthetized and intubated in the usual way and then placed on the cooling blanket and the blanket is then closed and the circulation of freezing mixture is begun. The temperature falls as shown in this chart (Fig. 2) recording a Blalock's operation in a child of 5 years.



Westminster Hospital Photographic Department.

FIG. 1

At 80° F. (27° C.) the anæsthetic is discontinued and 100% O_2 used for the inflation. Shortly afterwards operation is begun.

The following points seem worthy of brief note, but I hope I may be forgiven for putting these conclusions on such a small number of cases.

(1) The pulse-rate falls in this instance to between 30 and 40. Continuous ECG control was used and no worrying cardiac abnormalities were seen, despite the bradycardia—which I feel to be far less worrying than the tachycardia so common in these cases when conventional anæsthetic methods are used. I think that the well-known effect of too low a temperature leading to ventricular fibrillation does not necessarily connote increased cardiac irritability. Mechanical stimuli have not produced any cardiac irregularities.

(2) Despite cessation of the cooling circulator and even substitution of warm fluid, the child's temperature continues to fall for half an hour or so. If this is not borne in mind the desired level may be overshot.

C

(3) These blue babies become pink when well cooled. It is a great comfort to be able to inflate them with 100% oxygen. One has to balance the reduced metabolic demand for O_2 against the reduced oxyhæmoglobin dissociation at low temperature—we feel that this balance is favourable to the method.

(4) Reduced bleeding in the operative field is *not* a feature of this method, indeed the blood clotting time is trebled at this temperature—this has not seemed to lead to increased bleeding and may reduce the tendency to thrombosis in these cases.

(5) The simplicity and rapidity of producing hypothermia by external cooling in this manner is very pleasing and one feels, therefore, that in children it is preferable to extra-corporeal circulation and cooling. We have been very happy with the anæsthetic, operative, and post-operative course of these cases and feel that this is probably the anæsthetic method of choice for them.

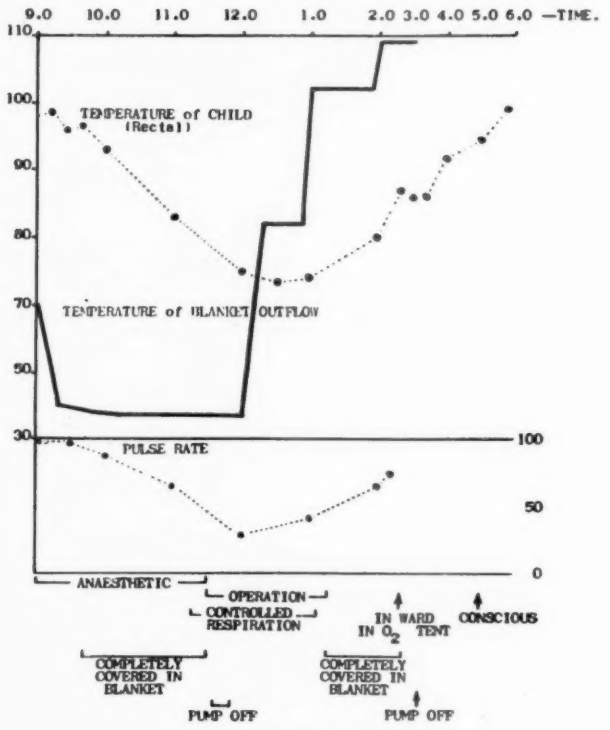


FIG. 2 (Dr. Scurr's case)

Dr. G. Vourc'h (of Paris): The term Artificial Hibernation, such as is used by some French writers, is most confusing and, in my opinion, ought to be abandoned as cold plays little part in the technique. The whole concept is very vague; it seems to me they are trying to force the facts to fit their theory. Their claims of wonderful results do not stand careful investigation: they assume that most of the cases were lost anyhow; therefore, should they die, it would be in spite of the technique; should they survive, it is because of it. One hears a lot about the successes, and hardly at all about the failures, which are, nevertheless, real. Their figures do not substantiate their claims: 30% mortality is very high, artificial hibernation or not.

What, in all this, is the place of Largactil, or chlorpromazine, is hard to tell. Some of the claims made for it are wrong; for instance, it has been presented as ganglionic blocking, which it is not. It would be a pity if an interesting drug should fall in discredit because of these fantastic claims; it is certainly worth careful, scientifically conducted clinical investigations. One thing is certain: it is a strong central depressant and nearly all its actions can be attributed to this; it has its place among many other drugs to achieve one purpose, i.e. sedation. Apart from that, there is no evidence that it can work miracles by itself through some obscure "lytic" or "disconnecting" action. Because it is such a strong depressant, it may hide the patient's true condition; treating the symptom is not always curing the disease. What criteria, for instance, persuade a ward sister to say that "a patient does well under Largactil"? It may be, of course, that he is in fact very well; but it may be also that she finds he is well only because he is in a state of semi-stupor, with a low temperature and no cough, because the regulating mechanisms and reflexes are depressed. As Dr. Beard has pointed out, it is sometimes surprising to find that suction brings up quite a lot of unsuspected sputum.

Some good anæsthetists in France are still trying the drug and assessing what its real position in anæsthesia should be. To some it seems that its indications are medical rather than surgical: severe hyperthermia, encephalitis, cerebral hæmorrhage, mental cases, etc. Refrigeration of the whole body offers probably more scope in cardiac surgery than Largactil does; it can be achieved without it, and Dr. Juvenelle seems to think that the toxicity of the drug is too big at low temperatures to be used safely for that purpose.

Dr. D. A. B. Hopkin: Dr. Bernard Kenton drew my attention to the possibilities of the phenothiazine derivatives in anæsthesia three months ago, and since then he and I have administered them either singly or in combination to over two hundred patients; many poor risks, mostly elderly, and a few in hæmorrhagic shock.

For patients undergoing operations of moderate severity, premedication with promethazine/pethidine/atropine replaces the well-known Omnopon/scopolamine. Pre-operative sedation is excellent. Patients are calmer, and more drowsy than with the older methods. Anæsthesia is smooth and easy, and is remarkably free from respiratory disturbance and depression. The dose of Pentothal is reduced by 20%, and the effect of nitrous oxide seems to be enhanced.

The post-operative condition of these patients is a subject of favourable comment by experienced ward sisters. Restlessness and vomiting are rare, and nursing is much easier. On the day following operation patients appear fresher and more alert. These are admittedly only impressions, but being backed by unanimously favourable nursing opinion in different hospitals we consider they are significant.

For poor risks, and all major operations, we have used a combination of promethazine, chlorpromazine, pethidine, and atropine. We have made no attempt to induce hypothermia. We have been impressed by the ability of patients under the influence of these drugs to withstand severe trauma without showing the signs of shock that one would normally expect. We have also found that our calls on the blood transfusion services have been reduced, during and after operation. Post-operative condition is excellent and many patients require no sedation in the immediate post-operative period.

Since we have been using chlorpromazine we are more prepared to accept risks which formerly we would have refused. Our reason for doing this is based on the feeling of security from the development of operative shock of a severity likely to prove fatal, especially in elderly patients who have to undergo radical operations for extensive malignant disease.

Our knowledge of the pharmacology of these drugs, especially chlorpromazine, is still incomplete. The central action of the latter is extremely interesting, and in the absence of exact information is likely to give rise to considerable speculation. There is no doubt, however, that its elucidation may enable us to obtain a clearer picture of the pathogenesis of the various manifestations of shock.

We may have to revise particularly our present views about the changes which occur in the peripheral circulation, and the factors which influence vasomotor tone.

Apart from these theoretical considerations we consider that from a practical point of view these drugs are of real benefit to both patient and anæsthetist, and are an important advance in anæsthetic technique.

Dr. David Morris: In a recent visit to Paris it was my good fortune to see artificial hibernation used in clinical medicine (Morris, 1953, *Lancet*, ii, 1039). In premature infants, ill from birth injury or hyaline membrane of the lung Largactil was given by mouth in hourly divided doses of 1–2 mg. per kilo per day continued for four to five days; the dose was regulated for the effects of "disconnection" rather than hypothermia. It was also being used on children very ill with infections not responding to the standard methods of treatment; in these a mixture of Largactil, pethidine and phenobarbitone was given intravenously. The use of Largactil in the treatment of congenital pyloric stenosis illustrates its valuable anti-vomiting properties. This new method of treatment, applicable in a variety of clinical conditions is surely worthy of further trial whereby we will learn in more detail its evaluation.

Dr. O. P. Dinnick: I have been using Phenergan as an additional drug for premedication for about three years, and would like to support previous speakers in affirming its usefulness. I have found it valuable for three reasons.

Firstly, in the anæsthetic management of asthmatics and chronic bronchitic patients with bronchospasm and a hyperactive cough reflex. Although Phenergan has not proved to be of great value in the clinical management of these cases, there is no doubt that premedication with this drug makes them much more controllable under anæsthesia. Not only, as noted by other speakers, are the laryngeal reflexes less active, but even more noticeable, there is much less tendency for bronchospasm to occur in response to anæsthetic or surgical stimuli. For example, after Phenergan in this type of case, nitrous oxide, oxygen and ether inductions—even by inexperienced students—have been remarkably smooth, when normally much difficulty would be expected.

Secondly, when extra pre-operative sedation is required, especially in those patients who are accustomed to taking large doses of barbiturates, or when it is desired to avoid the uncertain cumulative effect of mixed barbiturate medication.

Thirdly, for its anti-emetic value. Dr. Beard has mentioned the many difficulties involved in evaluating this attribute of a drug and I will not elaborate them. However, my impression is that this property of Phenergan is a very real one. My most convincing evidence comes from a group of patients who have had multiple operations of similar magnitude, some of whom now demand the drug pre-operatively.

I have given a dose of 50 mg. for the average adult patient, administered by mouth about three to six hours before operation. I have seen no alarming falls of blood pressure or other untoward effects which could be attributable to the drug, and in only one case was post-operative stupor sufficiently deep and prolonged as to give rise to comment. This case caused no anxiety, however, and had also received relatively large doses of other depressant drugs.

[*February* 5, 1954]

General Anæsthesia for Out-patients, with Special Reference to Dental Extraction

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Addendum

Since this paper was read it has been established (Newton-Andrews, 1954; Bourne, 1954) that under certain conditions it is possible to strike sparks when dental forceps slip. Cyclopropane should not, therefore, be used in anæsthesia for extraction of teeth until this matter has been fully investigated (Bourne, J. G., 1954, *Brit. med. J.*, i, 937; Newton-Andrews, H., 1954, *Brit. med. J.*, i, 641).

Critical Review of Nitrous Oxide

Nitrous oxide has long been the mainstay of anæsthesia for out-patients. I have criticized this use of nitrous oxide, arguing that its low potency, usually regarded as an advantage, is, in fact, a disadvantage. Contrary to current belief, a narcotic of high potency, I suggested, might be not only more effective but also safer, and my experience with cyclopropane led me to think that more nearly than any other agent it met the requirements of out-patient work (Bourne, 1952).

Continuing this study, I thought it worth while to make a fresh clinical assessment of the potency of nitrous oxide. For this purpose I anæsthetized 60 unselected adult in-patients in the following way: They were premedicated with hyoscine, or, if they were over 60, with atropine. Anæsthesia was induced with 50% cyclopropane in oxygen breathed for thirty seconds from a 6 litre bag. During this inhalation suxamethonium (Scoline) was injected and as soon as the jaw relaxed a cuffed tube was inserted into the trachea. Anæsthesia was then continued with nitrous oxide and oxygen, given at first by artificial respiration, and time was measured from the start of this inhalation.

At ten minutes both the suxamethonium and the cyclopropane had disappeared and the nitrous oxide had developed its maximum effect or nearly so. From then on the patients' reactions and behaviour were noted and the effect of nitrous oxide was assessed.

Film on nitrous oxide.—At this point was shown a silent, coloured film demonstrating the effects of endotracheal nitrous oxide-oxygen anæsthesia in 6 adult patients.

The first 2 patients, a man of 75 and a healthy, muscular, teetotal Scotsman of 26, were seen to be in light surgical anæsthesia under 80% and 83% nitrous oxide, respectively. The flow-rates were:

$$\frac{N_2O}{O_2} : \frac{8}{2} \text{ and } \frac{10}{2} \text{ l./min.}$$

The second 2 patients, a woman of 32 weighing 5 st. 10 lb., suffering from Crohn's disease with chronic diarrhœa treated for years with cret. c cpio, and Tab. Codein. Co., and a man of 39 who was a moderate beer drinker, were shown reacting briskly to minor painful stimuli. They were semi-resistant to nitrous oxide.

The third 2 patients were resistant to nitrous oxide. They remained alert and active, making purposeful movements and did not seem to have lost consciousness. The flow-rates for this and the previous pair of patients were:

$$\frac{N_2O}{O_2} : \frac{10}{2} \frac{(83\%)}{(17\%)} \text{ l./min.}$$

Of the last 2 patients the first was a drayman, aged 48, who drank 5 pints of beer daily. In the second, a man of 57, also a beer drinker, anæsthesia did not appear to become appreciably deeper, though he became cyanosed, when at 15 minutes the flow rates were changed for 4 minutes to:

$$\frac{N_2O}{O_2} : \frac{10}{1} \frac{(91\%)}{(9\%)} \text{ l./min.}$$

When after ten or more minutes, the brain had become saturated, how effective really was nitrous oxide? I will now extend the few observations of the film with my account of 60 cases. Of these 60 unselected adults, 27 of them women, 21 were over 60 and 11 over 70 years old. Few drank much alcohol, and judged by the usual criteria the sample contained only 2 or 3 who might have been expected to be resistant to anæsthetics. Yet, of the whole sample, only 1 in 4 reached surgical anæsthesia with nitrous oxide and these only the lightest plane of it. In a further 1 in 4 I could not feel

convinced even of unconsciousness, though they remembered nothing. In 3 of these, accidental disconnexion from the apparatus for not more than 3 or 4 breaths was sufficient to restore not only memory but also a considerable degree of mental orientation. More than half the sample retained reflexes that were too brisk to allow even minor, superficial operations.

All these patients were considered after ten or more minutes. Suppose I had been able to observe them at, say, two minutes; what could I have expected? Saturation of the brain takes time; clinical observation suggests seven to fifteen minutes (Mushin, 1952; Kaye, 1951).

Kety and Schmidt (1945) have measured this time and Fig. 1, taken from their paper, shows that in a human subject breathing 15% nitrous oxide the brain was not completely saturated for 20 minutes. At 2 minutes, though arterial blood was well on the way to saturation, internal jugular blood, and therefore brain tissue, was barely one-third saturated. In apes breathing 40% nitrous oxide they found a similar lag and it seems probable that in man breathing high concentrations the same trends and time relations would be seen. At 2 minutes, therefore, it is likely that not a single patient would have entered surgical anæsthesia.

But in the out-patient dental clinic how long, in fact, does the expert with nitrous oxide wait for the effect? In 1944 Dr. Marston (1945), speaking here on nitrous oxide anæsthesia in the dental chair, said: "Between the 14th and 20th breath the signs of surgical anæsthesia will be recognized"—that is, in one minute or less with 100% nitrous oxide. And in a clinic where this method is taught I recently observed that of 100 consecutive patients, in 70 both the anæsthetic and the operation were completed within two minutes.

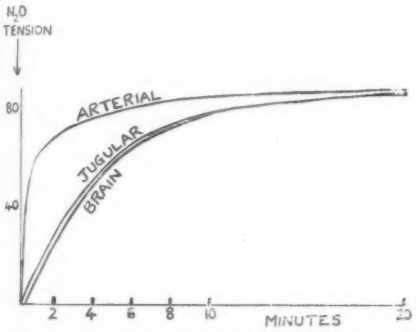

FIG. 1.—Arterial and internal jugular blood tensions and the calculated brain tensions of nitrous oxide in a human subject during inhalation of 15% nitrous oxide in oxygen. (N_2O tensions in mm.Hg.) After Kety and Schmidt (1945). By permission of the authors and publishers, Messrs. Williams and Wilkins, Baltimore, U.S.A.

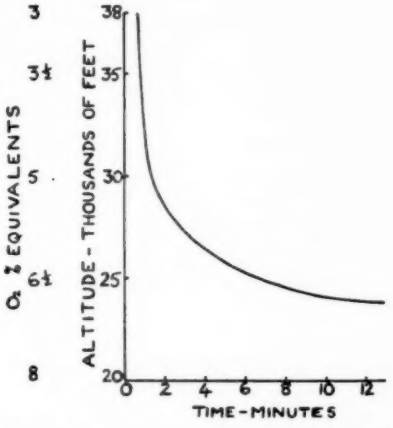

FIG. 2.—The time to unconsciousness in healthy young adults at rest at various altitudes due to sudden loss of oxygen supply. Sea-level oxygen percentage equivalents are shown on the left. Modified from Armstrong (1952). By permission of the publishers, Messrs. Baillière, Tindall and Cox Ltd., London.

Why does it work? In my opinion the answer is to be found in Armstrong's book on aviation medicine. " . . . a man at rest", wrote Armstrong, "can hold his breath for 1 to 1¼ minutes. But if the oxygen in the lungs and blood is washed out by breathing any inert gas such as nitrogen, sudden and complete loss of consciousness will occur in about 50 seconds" (Armstrong, 1952*a*).

Fig. 2, modified from Armstrong, shows in healthy young adults at rest the time taken at different altitudes for consciousness to be lost when the subjects were suddenly cut off from their oxygen supply and left breathing air. Against each altitude I have set its oxygen percentage equivalent at sea level. Thus, at 38,000 ft., or at sea level when 3% oxygen in nitrogen was breathed, consciousness was lost in less than a minute; and at 30,000 ft., or at sea level with 5% oxygen, in just under two minutes (Armstrong 1952*b*).

I believe we are left with no other reasonable conclusion than that the expert with nitrous oxide, knowing the trick, induces "anæsthesia" rapidly by taking his patients straight to 30 or 40 thousand feet. From there he allows them to descend only so long as they behave themselves and then only at a rate that is compensated by the accumulation in the central nervous system of increasing quantities of nitrous oxide.

In Fig. 3 I have tried to represent in its true colours nitrous oxide-oxygen anæsthesia when administered to the small group of patients who are not resistant to it. The horizontal line, LA, marks the entrance into light anæsthesia. This is reached by the summation of two effects indicated by the curves, namely, anoxia plus nitrous oxide. (These curves represent, not concentrations, but depth of anæsthetic effect.) At first, anoxia predominates and induction is mainly but not entirely due to that influence. Then, as nitrous oxide accumulates in the brain, more and more oxygen can be added and anoxia is gradually relieved. Eventually anæsthesia runs smoothly along on 80% nitrous oxide and oxygen.

In these people, with patience, it is sometimes possible to reach anæsthesia using 20% oxygen from the very start. This small group can be increased in number if nitrous oxide is boosted with trichlorethylene (Trilene) or other volatile agent.

Fig. 4 represents the character of anæsthesia in patients whom I have called semi-resistant. In these, who form the largest group, nitrous oxide goes less far. Induction is again anoxic but more so and anoxia can be less quickly relieved. It is probable that most dental extractions are completed before the curves cross. But even when the administration is prolonged oxygen deprivation cannot be altogether dispensed with. This was admitted by Clement, who succeeded McKesson at Toledo and is one of the foremost exponents and advocates of nitrous oxide anæsthesia. "The production of anesthesia with nitrous oxide", he wrote, "necessitates a restriction of the oxygen in the majority of instances" (Clement, 1951*a*). And Kaye (1951) found that in more than half his patients there had to be "gross restriction of the supply of oxygen".

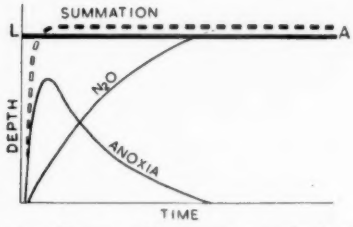

FIG. 3.—Nitrous oxide-oxygen anæsthesia in a patient of low resistance.

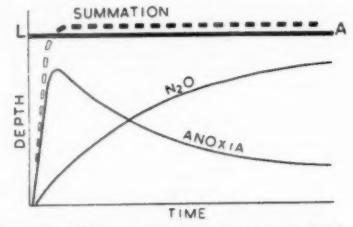

FIG. 4.—Nitrous oxide-oxygen anæsthesia in a patient of average resistance.

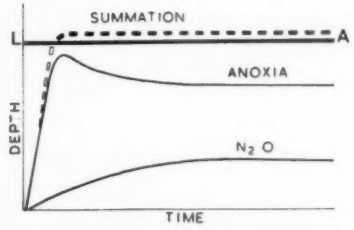

FIG. 5.—Nitrous oxide-oxygen anæsthesia in a patient of high resistance.

But these diagrams represent anæsthesia when anoxia is employed throughout to the least possible extent. This is the ideal that is aimed at but the requirements are seldom hit off so accurately as that. Frequently, the curve of anoxia alone extends well up into the territory of anæsthesia, and, when jactitations occur, the summation curve might go above the top of the screen. At that juncture anoxia is apt to be over-corrected and summation may then fall below the line, LA. "Control of anesthesia", wrote Clement (1951*b*), "is synonymous with control of the oxygen." " Often as little as 1% perceptibly alters the depth of narcosis" (Clement, 1951*c*).

I have referred to resistance. This is of two kinds, which I call "false" and "true". "False resistance" is seen during induction in the delirium of a man who is not minded to take it lying down. He struggles. This same man, however, once saturated with nitrous oxide, might be quietly anæsthetized without anoxia, like the teetotal Scotsman shown in the film. "True resistance", on the other hand, is seen in the patient who is barely unconscious even when saturated with 80% or 90% nitrous oxide. "False resistance" is a product of temperament and training; "true resistance" seems to come from habituation to narcotic drugs. Perhaps this explains why true resistance is unusual in children, and in young men and women who are teetotal, and is more commonly encountered in middle-aged or elderly patients—patients in whom deprivation of oxygen would seem most unwise. "The essentials for success

during induction (in the resistant group)", wrote Clement, "are . . . the minimum of oxygen in the mixture, the time element and a disregard of cyanosis" (Clement, 1951*d*).

Fig. 5 represents nitrous oxide anæsthesia in the resistant group. But it does not indicate the deterioration that sets in when anoxia is prolonged and severe. It does not show how, in the words of our President, an A 1 may be converted into a C 3 man and how, by this means, the really difficult patient can be forced into the range of nitrous oxide anæsthesia. Anoxia of this severity does not leave much room for bungling.

Lewis and Haymaker (1948) investigated 75 deaths from high altitude anoxia in American airmen. The exact duration of the anoxia was known in 6. In 4 of these it was 3 minutes or less. Of course, had an expert with nitrous oxide been present to press an oxygen button at the moment of respiratory arrest the situation would have been retrieved. Doubtless, the number of patients who have been rescued in this way in the dental chair is very great; but Courville and others have shown that on occasions the anoxic decerebration of nitrous oxide anæsthesia can become irreversible.

The cases that Courville investigated fell into three groups. In the first group the anoxic damage to the brain was so severe that, either immediately or after a lapse of hours or days, the patients died. In the second group the damage was less severe. These patients survived but were demented and had to be certified insane. Of the third group Courville wrote: "These patients go through an anoxemic episode, present dramatic and alarming symptoms shortly thereafter, but recover more or less promptly, apparently little the worse for the experience" (Courville, 1939).

Now, if some patients are killed and others demented, is it likely that all the rest get off scot-free? Is it too far fetched to suppose that there may, on occasions, be some loss of the brain's considerable reserves which, though it passed unnoticed, might be obscurely reflected in future mental performance?

Whether or not these speculations are justified it must be admitted that, whereas it is now an accepted principle of in-patient anæsthesia that anoxia is harmful and to be avoided, in out-patient practice anoxia is still employed by all and sundry as a supplementary agent of anæsthesia. Perhaps it would be more truthful to say that anoxia is the main and nitrous oxide the supplementary agent.

Cyclopropane

A silent, coloured film illustrating the conduct of anæsthesia with cyclopropane in 5 patients was then shown. The film demonstrated the apparatus, including a special angle-piece incorporating a two-way stop-cock and an expiratory valve, and the filling of a large reservoir bag with 50% cyclopropane in oxygen.

With this bagful of cyclopropane and oxygen I have anæsthetized without mishap, 1,918 patients of all ages, from infants to those in their eighties. This number includes the 1,000 that I reported previously (Bourne, 1952). No walking patient was refused and there were in addition several who were bedridden because of recent coronary thrombosis or other serious cardiovascular disease and who were rightly considered unsuitable subjects for nitrous oxide.

Other anæsthetists have tried cyclopropane for ambulatory patients, but after initial enthusiasm became disappointed and gave it up or reserved it for patients in whom nitrous oxide was unsuitable. Disadvantages, they found, were salivation during induction, delay in recovery, and a high incidence of nausea and vomiting. Of these disadvantages I encountered only the last, and this I have recently found ways of reducing.

This difference between my experience and that of my colleagues might be explained by the concentration and quantity of cyclopropane that I used and the speed with which it was given. My patients inhaled 50% cyclopropane in oxygen from a so-called "3 gallon" bag, the actual capacity of which was, in fact, 1·3 gallons. (A bag any smaller than this held an insufficient dose and gave unsatisfactory results.) Induction was very rapid. All patients lost consciousness in 3 to 6 breaths and after a few more breaths were ready for operation. By this means a maximum effect was produced with a minimum amount of drug, the brain receiving a high proportion of what was given as when a small dose of thiopentone (Pentothal) was injected quickly. My colleagues, on the other hand, possibly gave cyclopropane more slowly and in lower concentration in oxygen or as a supplement to nitrous oxide and oxygen. The drug would then be more evenly distributed in the body, forming depots in fat and other tissues which, on account of their poorer blood supply or lower lipoid content, would not receive much cyclopropane when it was given quickly. Administered slowly, a greater quantity would have to be given to produce the same effect. Induction being slower, salivation and vomiting might well occur at that stage, and recovery would be delayed as when anæsthesia was induced by the slow infusion of thiopentone.

A small disadvantage that I found in this rapid induction was excitement which occurred after loss of consciousness and was quite different from the delirium seen with nitrous oxide. It appeared as a tonic contraction of muscles followed by clonic movements. Sometimes it was sufficiently marked to displace the patient in the dental chair, but provided it did not inconvenience the surgeon the extractions could be proceeded with. My previous report described this excitement together with the electro-encephalographic findings. As part and parcel of it momentary breath-holding commonly occurred which was ascribed by Guedel (1940) to depression of the respiratory centre. I gave three

reasons for thinking that Guedel's interpretation was incorrect, and in experiments in which I left cyclopropane and oxygen flowing into the bag during the inhalation, each at 1,500 c.c. per minute, and absorbed the carbon dioxide with a Waters' cannister, I found, in fact, that only after 4 to 7 minutes did respiration show the effects of narcotic depression, which was gradual in onset and slowly progressive—quite unlike the sudden respiratory arrest that sometimes occurred with thiopentone or ethyl chloride. In no patient in my series was respiratory depression encountered.

In no patient, moreover, did vomiting occur during induction. But nausea, sometimes with vomiting, was a symptom that frequently marred recovery and occasionally, in my earlier cases, lasted for hours. Of my first 1,000 patients 21% vomited and a further 12% suffered nausea. But in these patients I left the bag attached to the machine and, with cyclopropane and oxygen flowing at 1,500 c.c. per minute, often continued the inhalation for much longer than I now find necessary. Many of them had no premedication and those to whom I gave hyoscine had only a small dose. By contrast, my last 150 patients were all given 1/75th grain of hyoscine by mouth, or, if they were under 14, half that dose; and the inhalation of cyclopropane was limited to 1 minute or less. Of these 150 only 8% vomited, never more than once, and a further 3% complained of nausea which was transient.

Inhalation for 1 minute or less gave satisfactory operating conditions which lasted about 2½ minutes. This was more than sufficient in most cases. There remained, however, the difficulty of extending this time when required. Formerly, I did this by renewing the inhalation of cyclopropane and oxygen, and I repeated this as often as necessary. Recently, I have found it more satisfactory to administer nitrous oxide and oxygen immediately following induction with cyclopropane. Thus, during the time that the patient is anæsthetized with cyclopropane, the opportunity is taken of reaching partial saturation with nitrous oxide; and since cyclopropane does not disappear abruptly from the body, this drug continues for a few minutes longer to support nitrous oxide. This sequence resembles the method of anæsthetizing out-patients by the rapid injection of a small dose of thiopentone followed by nitrous oxide. But it has the advantage of being more easily administered and more transient in effect.

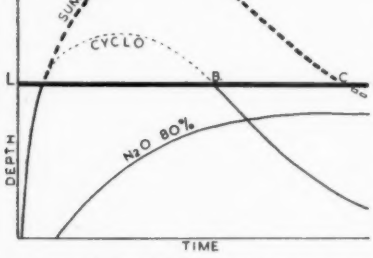

FIG. 6.—Prolongation with nitrous oxide of anæsthesia induced with cyclopropane in a patient of average resistance.

Fig. 6 shows how in a patient of average resistance the period of anæsthesia with cyclopropane can be extended with nitrous oxide and oxygen. Had cyclopropane alone been used anæsthesia would have ended at "B". In this patient it was possible to extend it to "C". In a patient of low resistance it could have been extended indefinitely. At the other end of the scale, however, in the resistant group, nitrous oxide would have been of little help.

There remains the problem of handling as an out-patient for difficult dental extractions the really resistant patient. The only satisfactory solution here is endotracheal anæsthesia with the throat packed. Intubation can be easily performed in the dental chair if suxamethonium is injected immediately following a small dose of thiopentone. Anæsthesia can then be continued with nitrous oxide and oxygen on an open circuit and further doses of suxamethonium can be added if necessary. In this way good operating conditions can be safely and indefinitely prolonged.

Comparison of Nitrous Oxide and Cyclopropane

While operating conditions are satisfactory with cyclopropane and not always so with nitrous oxide, this is not the only consideration. There is also the patients' point of view. In the whole series of 1,918 patients, 351 adults had previously been given nitrous oxide and were able to compare their experience of the two anæsthetics. In spite of the fact that nausea occurred less frequently with nitrous oxide, 4 out of 5 of these patients expressed preference, usually in strong terms, for cyclopropane. In reply to this critics have reminded me that I did not know who had given the nitrous oxide; it might, they said, have been given by those with little experience. Do these critics suggest that four out of five times, or even only once out of five times, nitrous oxide was badly given? If so, the fault may lie in the method; perhaps it is too difficult. With cyclopropane it did not matter who gave it provided he could safely give an anæsthetic and was capable of holding an ill-fitting mask on a badly shaped face—a problem that I have in hand with the instrument makers.

In this comparison unexpected facts came to light. Several patients preferred cyclopropane because they felt much better after it than they did after nitrous oxide. One middle-aged man was given nitrous oxide for the extraction of a single tooth. For two hours he remained unconscious or semiconscious and for two days was unable to conduct his business and did not feel that he could safely drive his car. As he could afford the best, his anæsthetist was one of the many who are expert at this kind of work. Since this anæsthetist had departed before he regained consciousness it was left to the dentist to tell

him that he must never be given gas again. This puzzled him because he had often had nitrous oxide and rather liked it. He enjoyed the exhilaration of having a bit of a fight going under. As usual, this episode was not reported in the literature.

Other patients disliked nitrous oxide because it did not make them fully unconscious. They preferred cyclopropane because with it loss of consciousness was pleasant, immediate and complete.

In 37 patients nitrous oxide anæsthesia had totally failed. This is not surprising. The field of surgical anæsthesia offered by the method is very narrow; on one side is delirium, on the other anoxia in dangerous excess. In some patients the territories of delirium and of dangerous anoxia overlap and there is then no safe field of surgical anæsthesia. This may be illustrated by three further statements by Clement:

> "... nitrous oxide-oxygen anesthesia", he wrote, "... may be very dangerous in the hands of the novice. The margin of anesthesia ... is very narrow ..." (1951*e*).
>
> "... the transition from the light to the deep or even profound plane may occur with bewildering rapidity" (1951*f*).
>
> "Alcoholics usually resist the anesthetic strenuously for a time and then, not infrequently, a sudden drop into the dangerous fourth plane may occur with little or no warning" (1951*d*).

Unlike nitrous oxide, cyclopropane can be accompanied from the start by oxygen at a concentration greatly in excess of atmospheric. With cyclopropane, the field of surgical anæsthesia that lies between too light anæsthesia on the one hand, and respiratory depression on the other, is wide and traversed slowly. It is easy to know when this field has been entered and there is plenty of room within it for light anæsthesia without risk of getting patients too deep. For these reasons, cyclopropane is probably the easiest of all anæsthetics to administer safely and effectively to out-patients.

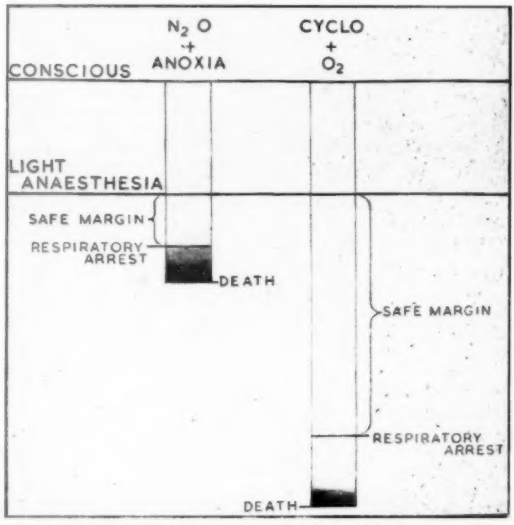

FIG. 7.—The relative margins of safety with nitrous oxide and cycloprane. Cyanosis is represented by shading.

In Fig. 7 I have contrasted what I consider to be the safe margins with the two methods. My purpose is to draw attention less to the narrow margin with nitrous oxide than to the broad one with cyclopropane. For it is, in fact, astonishing that a method inherently so unsound as that with nitrous oxide should prove in practice to have a mortality so low. From the Registrar-General's reports (1953) it seems that in twenty-one years only 1,313 patients in England and Wales had been killed by it—an average of little more than 1 a week. Other Government statistics (Ministry of Education, 1952; Ministry of Health, 1952) show the enormous number of administrations of general anæsthesia for dental extraction alone. These amounted in England and Wales to more than 2,000,000 annually, and even this figure did not include all administrations for dental extractions and left out minor surgery of other kinds. Nitrous oxide, of course, was not the only agent used, but it was probably the main one. Judged by this crude measure of mortality alone nitrous oxide must be deemed satisfactory. It is therefore most necessary that any alteration that is proposed in the hope of improving work in this field should, before it is recommended for general adoption, be given the most thorough

clinical trial. The opportunities for mass manslaughter are great. Every care must be taken to make quite certain that no possible danger is overlooked.

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Dr. Victor Goldman felt that it was not scientific to assess the potency of nitrous oxide and oxygen mixtures after inducing the patient with a mixture containing 50% of oxygen and an injection of Scoline which would prevent the oxygen being blown off for some time.

Dr. Clement had frequently stated that most failures to produce effective and safe anæsthesia with nitrous oxide and oxygen were caused by either giving too much oxygen in the early stages or not enough later on. Dr. Goldman recalled the cases personally anæsthetized by Dr. Clement at the Eastman Dental Hospital in 1953 when after intubation and packing his cases were carried with increasing percentages of oxygen, always over 50% and in 1 case over 75%. Dr. Goldman warned Dr. Bourne that to continue a mixture of 20% oxygen with nitrous oxide over a long time would in itself produce under certain circumstances anoxia and cerebral damage far greater in the fit individual than the momentary anoxia which may arise during induction.

Cyclopropane was not without danger, its action upon the heart even during short cases could be shown by the electrocardiogram to be undesirable, and whereas for induction it might prove useful it had little to offer over the well-known technique of induction with a small dose of an intravenous barbiturate. Dr. Goldman said that eighteen years before he had himself stood in the same meeting place to claim that he had the perfect short anæsthetic in Vinesthene which could be given with 100% oxygen. Nowadays, however, he only used that agent for the difficult child who could not be made to sit in the dental chair without struggling. In the same way he felt that cyclopropane might find a small but useful place in out-patient anæsthesia, after its trial by trained anæsthetists.

Dr. R. Blair Gould thought the anoxic factor in dental nitrous oxide-oxygen anæsthesia had been much exaggerated—it was not impossible to avoid anoxia completely in most cases. Difficult patients were dealt with satisfactorily if suitable premedication was given. The virtues of nitrous oxide were those very properties which the lecturer deplored, viz. its lack of power and lack of toxicity, which made it eminently suitable for out-patient minor surgery, particularly in dentistry, although Dr. Gould agreed with Dr. Bourne that alone it was unsuitable for in-patient major surgery. On the other hand cyclopropane was a very toxic and powerful drug, with profound physiological effects from which out-patients took some time to recover. His experience was that dental patients did not feel so well, nor were they so capable of resuming their work, after this drug as after nitrous oxide. In his opinion the use of such an undoubted tissue poison, in substitution for nitrous oxide-oxygen for out-patient dentistry, was a retrograde step.

Section of Experimental Medicine and Therapeutics

President—G. A. H. BUTTLE, O.B.E., M.A., M.R.C.S., L.R.C.P.

[*February* 9, 1954]

DISCUSSION: GASTRIC BIOPSY AND THE INVESTIGATION OF THE MEGALOBLASTIC ANÆMIAS

Dr. R. K. Doig (Walter and Eliza Hall Institute and Royal Melbourne Hospital, Melbourne, Australia):

Gastric Biopsy and Gastritis

Gastric biopsy tube.—The principle of the gastric biopsy tube is that when the stomach is empty sudden suction applied to one end of a tube will draw mucosa into the other end lying in the stomach. If a knife be now pulled across this hole a fragment of mucosa will be cut off. The tube is made of Bowden wire covered with plastic and ending in a stainless steel cylinder with a lateral hole. A small cylindrical knife is moved up and down by a flexible wire past the lateral hole. The details of design and an initial report on the use of this instrument have been published elsewhere (Wood *et al.*, 1949). Instruments based on the same principle have been used by Palmer (1950), Tomenius (1950) and Rubin *et al.* (1953).

The biopsy.—This is carried out with the patient in the fasting state. After anæsthetizing the throat, the stomach is emptied and the tube passed to an appropriate depth. The biopsy is carried out by pushing the knife down, applying sudden suction and pulling the knife up. The procedure is repeated before the tube is removed. The specimens are fixed and sectioned perpendicular to the surface. The sections are stained with hæmatoxylin and eosin or mucicarmine, and also by a method which stains the pepsinogen granules (Motteram, 1951). The biopsy procedure is successful in about 85% of attempts and has been done in a wide variety of clinical conditions, including duodenal ulcer, chronic gastritis and pernicious anæmia (Wood and Joske, 1954). The technique may be described as a "blind" one and therefore has no place in the direct diagnosis of gastric cancer. Biopsy is not done on patients who have a tendency to bleed. Bleeding has been the sole complication and in a thousand attempts was clinically evident in 8 patients, 3 of whom needed transfusion.

The appearance of the normal gastric mucosa may be described as follows. The surface and gastric pits are lined by a regular tall columnar epithelium. The gastric glands occupy the greater part of the mucosa and lie perpendicular to the surface. The lamina propria is small, blood vessels are not prominent and interstitial cells are few. The abnormal mucosal appearances are conveniently divided into superficial gastritis, atrophic gastritis and gastric atrophy (Motteram, 1951). In superficial gastritis there is inflammatory change confined to the superficial part of the mucosa, the surface epithelium may be flattened and the pits may be deeper than normal. There is a variable degree of infiltration of the lamina propria with inflammatory cells. In atrophic gastritis there is more extensive change histologically which, on clinical grounds, is of longer duration. Arbitrarily, atrophic gastritis is diagnosed when more than half the gastric glands are absent. The surface epithelium is irregular and there may be islands of intestinal metaplasia, the pits are longer and pseudopyloric glands are common. The gastric glands are irregular in their disposition in the mucosa. Cellular infiltration is variable, but is often intense with definite aggregations of small round cells. Gastric atrophy is typically found in pernicious anæmia (Magnus and Ungley, 1938). There are few or no chief or parietal cells, the surface epithelium is regular and either gastric or intestinal in type. The glands may resemble intestinal crypts with striated border and goblet cells, or form pseudopyloric glands. Cellular infiltration is much less than in atrophic gastritis but there is still an increased amount of stroma. The cells are mainly lymphocytes and plasma cells.

A single sample has been accepted as sufficiently representative of the whole body mucosa in the absence of a local ulcerative lesion of the stomach for the following reasons. First, when two fragments are removed either at the same time or a short interval apart they usually look alike; and studies of satisfactory operation or autopsy material show that gastritis of the body of the stomach is usually a diffuse lesion (Hebbel, 1949; Williams, 1950). Second, the results of the histamine test meal and the biopsy appearance are related: the less the gland content of the section the lower the acidity and output of gastric juice (Funder and Weiden, 1952).

The clinical findings in 112 patients with superficial or atrophic gastritis but without peptic ulcer or gastric cancer have been reviewed (Doig and Wood, 1952). Half of this group had dyspepsia of a definite pattern. They complained of abdominal pain often in the epigastrium. The pain is of varying intensity, occurring shortly after meals and not usually relieved by alkaline powder. Of this group of 60 patients nausea was reported by 19 and occasional vomiting by 21. Atrophy of the tongue and slight epigastric tenderness were common. Anæmia due to overt hæmorrhage was found in 11 cases and due to various other causes in 16 cases. 6 patients were admitted with hæmatemesis and melæna and one with melæna alone; only one of these patients required transfusion. Alcoholism was the only significant ætiological factor and was found in 19 cases. Resolution occurred in 5 of these but was infrequent in other cases.

Gastric atrophy is the characteristic lesion of the mucosa of the body of the stomach in pernicious anæmia. In a study of 46 patients with pernicious anæmia or subacute combined degeneration of the cord, only 3 were atypical and had atrophic gastritis. Conversely in only 2 patients was there gastric atrophy without anæmia or cord signs (Doig and Wood, 1950). The histological appearance of the mucosa is the same whether the patient is untreated, or has had treatment for a long time or at a high intensity (Finckh and Wood, 1953).

In summary: gastric biopsy is a simple and safe technique by which an adequate and representative sample of the mucosa of the stomach can be obtained. The histological appearance may be normal, or may show a superficial or atrophic gastritis, or gastric atrophy. Half the patients with gastritis had a recognizable clinical story of indigestion. Gastric atrophy was almost always found in patients with pernicious anæmia or subacute combined degeneration of the cord and the gastric lesion was unaffected by treatment.

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Dr. Adam Turnbull (Nuffield Department of Clinical Medicine, The Radcliffe Infirmary, Oxford):

Experiences with Labelled Vitamin B_{12}

My object in this symposium is to give an account of our experiences at Oxford with radioactive vitamin B_{12}. When, just over one year ago, Dr. Lester Smith sent us our first supply of vitamin B_{12} labelled with the radioactive isotope of cobalt Co^{60}, the only published observations with this material in man were those of Heinle, Welch and their colleagues at Cleveland (Heinle *et al.*, 1952). They had given 0·5 µg. doses of the vitamin by mouth to 4 patients with pernicious anæmia and to 2 normal subjects, and had estimated the radioactivity which appeared in the fæces. They found that a much greater proportion of the radioactivity of this dose appeared in the fæces of the patients with pernicious anæmia than in those of the normal subjects, unless a source of intrinsic factor was given with the labelled vitamin B_{12}. In a personal communication Dr. Welch indicated the difficulties which they had encountered owing to the low specific activity of the available radioactive B_{12}, about 60 µc./mg., and he said that workers in another unit had not been able to confirm their findings.

We decided that we should first make sufficient observations in control subjects and patients with pernicious anæmia to confirm or disprove the findings of the Cleveland workers. We decided to use the same dose of 0·5 µg., but we hoped to gain greater accuracy from the much higher specific activity, about 420 µc./mg., of our radioactive vitamin B_{12}. We have given this dose with the patient fasting, and have estimated by means of a scintillation counter the radioactivity which subsequently

appears in the fæces. Full details of the technique and of our early results have been published elsewhere (Callender *et al.*, 1954*a*).

The procedure was first carried out in 10 control subjects who were chosen to be of comparable age to our patients with pernicious anæmia. They were in hospital for a variety of complaints, for example peptic ulcer and hypertension, but apart from one who had a moderate iron deficiency anæmia in addition to a fractured femur, none had any evidence of any blood disease. In 23 tests on these 10 control subjects between 20 and 40% of the radioactivity in the 0·5 µg. test dose usually appeared in the fæces. The mean of these observations was 31% and the observed limits 14 and 47%.

In contrast, in patients with pernicious anæmia between 80 and 95% of the radioactivity in this dose of labelled vitamin B_{12} usually appeared in the fæces, the mean of 39 observations in 22 patients being 88% and the observed limits 74 and 101%.

Nearly all of these patients with pernicious anæmia were in remission under treatment with vitamin B_{12} at the time of the tests. It might be said therefore that the difference between the results in the control patients and the patients with pernicious anæmia was due to the tissues of the latter being saturated with vitamin B_{12} given by injection. Labelled vitamin B_{12} was therefore given with intrinsic factor to 7 patients with pernicious anæmia. As the source of intrinsic factor pooled neutralized human gastric juice (100 ml.) was used in 3 patients, extracts of human gastric mucosa, prepared by Dr. W. H. Taylor of the Biochemistry Department of the Radcliffe Infirmary, in 2 patients, and in 2 others Fraction B, an intrinsic factor concentrate prepared by Prusoff and his colleagues (Prusoff *et al.*, 1950) and kindly supplied to us by Dr. Arnold Welch. In every case the recovery of radioactivity was much reduced whenever a source of intrinsic factor was also given, and with the more potent preparations the recoveries approached those found in the control patients. We concluded from these results that the difference between the findings in the control subjects and the patients with pernicious anæmia was due to the failure of the latter to secrete intrinsic factor.

Observations were then made on patients who had undergone total gastrectomy. Our results are being reported in full elsewhere (Callender *et al.*, 1954*b*). Apart from one patient, the amounts of radioactivity which appeared in the fæces when labelled B_{12} was given alone were similar to those observed in the patients with pernicious anæmia. When a source of intrinsic factor was also given the recovery was always reduced. It seems that there is the same reduction or absence of the secretion of intrinsic factor after total gastrectomy as occurs in pernicious anæmia, and this supports the view that in man the stomach is the only gastrointestinal source of intrinsic factor. These patients are presumably living on their stores of vitamin B_{12} and they would not be expected to develop macrocytic anæmia until the stores are exhausted, a matter of about three years. In one patient the amount of radioactivity recovered was intermediate between the levels found in the controls and the patients with pernicious anæmia. It seemed that he secreted some intrinsic factor. Perhaps the gastrectomy was not strictly total, or possibly he had an island of ectopic gastric mucosa in the œsophagus which was secreting intrinsic factor. Such findings would account for the failure to develop macrocytic anæmia in some patients even for many years after "total gastrectomy".

A few observations have been made in patients with steatorrhœa and megaloblastic anæmia of pregnancy. The patients with steatorrhœa appear to fall into three groups. Normal recoveries were found in 3 in whom it appears that both the secretion of intrinsic factor and the absorption of vitamin B_{12} were normal. In 2 patients the recoveries were greater than we have come to expect in the normal, but were not reduced by the addition of intrinsic factor. It seems probable that there was some defect in absorption in these patients which was not due to lack of intrinsic factor. In one patient with severe steatorrhœa the recovery when labelled vitamin B_{12} was given alone was similar to that found in patients with pernicious anæmia, and it was greatly reduced when intrinsic factor was also given. Unfortunately only one such observation could be made but it appeared that there was a lack of intrinsic factor in this patient.

In 2 patients with megaloblastic anæmia of pregnancy the recoveries of radioactivity were within normal limits. Both were receiving folic acid at the time. We have found that in a patient with Addisonian pernicious anæmia giving folic acid does not affect the recovery of radioactivity after a dose of radioactive vitamin B_{12}. It is possible, however, that therapy with folic acid had caused the resumption of the secretion of intrinsic factor in these patients or its return to normal levels.

There are a number of points arising from these results. Most interesting, perhaps, are that the control subjects do not appear to absorb the whole of this small dose of vitamin B_{12}, and that the patients with pernicious anæmia appear to absorb a small part of it, about 10%. It must be emphasized, however, that it is the radioactivity of the Co^{60} atom which is being estimated and that this may not still be in a molecule of vitamin B_{12}. If breakdown of vitamin B_{12} does occur in the gastrointestinal tract degradation products containing cobalt might be absorbed. Finally it must be remembered that the test depends on the absorptive powers of the gastrointestinal tract at the

time at which the dose is given. These provisos notwithstanding, it appears that the technique provides a useful indirect measure of the secretion of intrinsic factor which it is hoped will assist in the further investigation of the role of vitamin B_{12} and of intrinsic factor in the megaloblastic anæmias.

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Dr. J. Badenoch (Nuffield Department of Clinical Medicine, Oxford): *The Use of Labelled Vitamin B_{12} and Gastric Biopsy in the Investigation of Anæmia*

In Oxford Dr. W. C. D. Richards and I have been using the flexible gastric biopsy tube to study the pathology of the mucosa of the stomach for about two years, and we are indebted to Dr. I. J. Wood and Dr. R. K. Doig and their colleagues for their help in the course of our work. We have been interested mainly in the changes which occur in the mucosa of the stomach in anæmia and in the correlation between our histological findings and the results of the assay of intrinsic factor as measured by the absorption of radioactive vitamin B_{12}.

Our method of carrying out the biopsy is similar to that already described by Dr. Doig. Our experience is not nearly so extensive as that of the Melbourne workers but we have attempted the procedure in over 160 cases and have obtained a specimen of gastric mucosa in 130 of these. In only one instance has the biopsy been followed by bleeding which was severe enough to be recognized clinically.

The specimens of mucosa from the body of the stomach obtained with our biopsy tube are about 2 mm. in diameter and they usually extend from the superficial epithelium to the muscularis mucosæ. In normal subjects histological examination reveals closely packed body glands containing numerous chief and parietal cells and very few cells can be seen in the interstitial tissue. In contrast in pernicious anæmia we find gross atrophy of the specific glandular tissue and no normal chief and parietal cells can be seen. In some there is confluent intestinal metaplasia. The degree of cellular infiltration in the interstitial tissue is variable but it can be quite marked. A similar picture is seen in patients with subacute combined degeneration of the cord even in the absence of a macrocytic anæmia.

We have had the opportunity to study 4 such patients in whom a provisional diagnosis of subacute combined degeneration of the cord has been made. In the first patient the diagnosis lay between subacute combined degeneration of the cord and disseminated sclerosis and in the second between subacute combined degeneration of the cord and hysteria. Neither had a megaloblastic anæmia. In both, the changes in the stomach resembled those found in pernicious anæmia and in both the absorption of radioactive vitamin B_{12} was impaired. This led us to make a firm diagnosis of subacute combined degeneration of the cord which was confirmed by the good response to treatment with vitamin B_{12}. In the third patient the stomach showed the changes of an atrophic gastritis but normal parietal cells were present in some numbers and the absorption of radioactive vitamin B_{12} was within our normal range. We felt that the diagnosis of subacute combined degeneration of the cord could be excluded with confidence.

The fourth patient, a boy of 15, was interesting because he was a strict vegetarian who developed a dietary deficiency of vitamin B_{12}. He suffered from classical subacute combined degeneration of the cord which responded dramatically to treatment with vitamin B_{12} alone. As might be expected from his history, both the results of gastric biopsy and the absorption of radioactive vitamin B_{12} were normal.

We believe that in pernicious anæmia there is a virtual absence of normal parietal cells in the mucosa of the stomach and if these cells can be found in any numbers the diagnosis should be carefully reviewed, and a search for other causes of megaloblastic anæmia such as intestinal strictures or occult steatorrhœa should be carried out. In fact in the patients in whom the biopsy findings have been anomalous the excretion of uropepsin and the vitamin B_{12} absorption studies have also indicated that the patient is not suffering from Addisonian anæmia.

However, in some patients without Addisonian anæmia but with achlorhydria, gastric biopsy revealed an atrophy of the specific glandular tissue which approached that seen in pernicious anæmia.

This stimulated us to look for other similar cases and we have been investigating all the patients in our wards who have histamine-fast achlorhydria. We were particularly interested to study patients with hypochromic anæmia and achlorhydria since this type of anæmia has been reported to be common in the close relatives of patients with pernicious anæmia.

We have carried out a gastric biopsy on 24 patients with hypochromic anæmia and achlorhydria and although the histological picture of the stomach appears to be very variable we have found 6 with a gross atrophy of the body mucosa, and 1 in whom the changes were indistinguishable from those found in pernicious anæmia. This last patient was very interesting. Two specimens of mucosa were obtained from her stomach and both showed the same changes, while further evidence that there was a generalized atrophy of the gastric mucosa was provided by the fact that the output of uropepsin in twenty-four hours was 32 units, which is well within the range we have observed in pernicious anæmia. She was a woman of 51 years of age who had had a severe hypochromic anæmia for seven years. She had lived on a bread-and-tea type of diet, she suffered from menorrhagia, and she had a smooth tongue, angular stomatitis and dysphagia. At the time of her admission to hospital her hæmoglobin was 55% with a colour index of 0·6. Her anæmia responded fully to iron by mouth and she has remained well for the past twelve months with no other form of treatment.

We have studied the absorption of radioactive vitamin B_{12} in the patients with hypochromic anæmia and achlorhydria who have gross atrophy of the gastric mucosa.

3 of the 6 patients in whom the degree of atrophy of the body mucosa of the stomach approached that seen in pernicious anæmia absorbed less of the radioactive vitamin than any of the control subjects we have examined so far, but in the 2 of these in whom the test was repeated with the addition of a source of intrinsic factor there was no significant difference in the result.

However, in the patient in whom the changes in the gastric mucosa were indistinguishable from those found in pernicious anæmia the absorption of radioactive vitamin B_{12} was greatly reduced and it could be restored to normal levels by the addition of intrinsic factor. There is every reason to suppose that this patient would develop pernicious anæmia in the future.

We have also used the gastric biopsy and the study of the absorption of radioactive B_{12} in the investigation of obscure cases of megaloblastic anæmia. Recently 2 young women with megaloblastic anæmia were referred to Professor L. J. Witts by the kindness of Dr. J. Lowe of Swindon and Dr. E. K. Blackburn of Sheffield. The clinical pictures they presented were remarkably similar.

Both were young women who suffered from epilepsy and both had received various anticonvulsants including Epanutin and phenobarbitone for the control of their fits. In both the presenting symptom of the anæmia was soreness and ulceration of the mouth and one was known to have a leucopenia at the time the symptoms developed. Both had been faddy about their food and neither liked meat, but neither had been on a strict vegetarian regime prior to the onset of the illness. The results of the investigations carried out in these 2 patients are summarized in Table I.

TABLE I.—SUMMARY OF INVESTIGATIONS CARRIED OUT ON 2 PATIENTS WITH EPILEPSY AND MEGALOBLASTIC ANÆMIA

(Dr. D. L. Mollin kindly estimated the levels of vitamin B_{12} in the sera)

Patient	Free HCl in gastric juice	% dietary fat adsorbed	X-rays gastro-intestinal tract	Gastric biopsy	% Co^{60} B_{12} in fæces	Serum B_{12} level
M. K., female aged 22	0	Normal 98%	Normal	Normal mucosa	Normal 17%	Low normal 120 μμg./ml.
B. C., female aged 17	+	Normal 95%	Normal	Normal mucosa	Normal 12%	Normal 215 μμg./ml.

The anæmia in 1 of these patients responded to vitamin B_{12} alone, while in the other folic acid was tried and a good response was obtained.

These 2 young women appear to us to be suffering from a hitherto undescribed form of megaloblastic anæmia. As judged by the result of the gastric biopsy and the absorption of radioactive B_{12}, neither is suffering from true Addisonian anæmia and we have done our best to exclude the recognized causes of intestinal megaloblastic anæmia. It is tempting to ascribe the anæmia to a dietary deficiency of vitamin B_{12} but the normal serum levels of vitamin B_{12} are hardly compatible with this hypothesis. In any event they present a different picture from that usually seen in a dietary deficiency of the vitamin in this country, for when such a deficiency occurs signs of subacute combined degeneration of the cord usually precede the onset of a megaloblastic anæmia.

It is remarkable that both of these patients were epileptic and we have been wondering if the anticonvulsant drugs they had received could have played a part in producing the anæmia. It is true that the barbiturates will inhibit maturation of red cells in marrow cultures *in vitro*, but these drugs are in common use to-day and it is hard to believe that such a toxic effect would have escaped clinical recognition.

We have no adequate explanation for the development of a megaloblastic anæmia in either of these patients but we hope that a combination of the study of the histology of the stomach with the absorption of radioactive vitamin B_{12}, and the estimation of vitamin B_{12} in the serum when applied to other puzzling cases, may help to solve some of the problems which still exist in the pathogenesis of the megaloblastic anæmias.

Dr. D. L. Mollin, and Dr. G. I. M. Ross (Department of Pathology, Postgraduate Medical School of London):

Vitamin B_{12} Deficiency in the Megaloblastic Anæmias

The previous speakers have shown that presumptive evidence of vitamin B_{12} deficiency may be obtained in certain patients with megaloblastic anæmia by means of gastric biopsy and by studies with radioactive B_{12}. If such patients are anæmic or suffering from neurological symptoms it is possible to confirm the presence of vitamin B_{12} deficiency by following their hæmatological or clinical response to treatment with the vitamin.

Vitamin B_{12} deficiency in patients with megaloblastic anæmia may also be recognized by demonstrating an abnormally low concentration of B_{12} in their serum. For the last three years we have been trying to determine the incidence of vitamin B_{12} deficiency in the various types of megaloblastic anæmia both by measuring the pre-treatment serum B_{12} concentration in these patients and, whenever possible, by following their responses to treatment with vitamin B_{12}, folic acid or folinic acid.

In this paper we summarize the results we have obtained. The sera from more than 280 patients with various types of megaloblastic anæmia have been studied. About 100 of these were patients at Hammersmith Hospital. Sera from the remainder were kindly sent by colleagues at other hospitals.

Methods

The serum B_{12} concentrations were measured by microbiological assay using the green alga *Euglena gracilis* var. *bacillaris* as test organism (Ross, 1952).

Details of the hæmatological methods have been given elsewhere (Mollin and Ross, 1952).

Results

Normal subjects.—The serum B_{12} concentration of 126 normal subjects ranged from 100 to 900 μμg./ml. The mean concentration was 360 μμg./ml. Similar concentrations in a smaller group of normal subjects were previously reported (Mollin and Ross, 1952).

Patients with pernicious anæmia.—The serum B_{12} concentrations of patients with untreated pernicious anæmia were much lower. The mean serum B_{12} concentration in each of 190 patients was less than 100 μμg./ml. In the majority of patients the concentrations were less than 50 μμg./ml.

In some of the less anæmic patients (R.B.C. 2·0 million per c.mm., or more) the serum B_{12} concentrations were between 50 and 100 μμg./ml. but the concentrations were still subnormal even in patients with normal or almost normal blood counts (Table I). For reasons given elsewhere we think that the serum B_{12} concentration only falls definitely below the normal range when the reserves of B_{12} in the tissues are almost exhausted (Mollin and Ross, 1953). We consider therefore that these patients are suffering from quite severe B_{12} deficiency in spite of their normal or almost normal blood counts. Such patients almost invariably complain of symptoms similar to those of treated patients with pernicious anæmia who are not receiving quite enough vitamin B_{12} to keep them in complete remission. When they are treated with vitamin B_{12} the slight abnormalities that may be present in their blood disappear, and even more definite change occurs in their clinical condition; there is an increase in appetite, weight and general well-being.

TABLE I.—THE BLOOD COUNT AND SERUM B_{12} CONCENTRATION OF PATIENTS WITH VERY MILD UNTREATED PERNICIOUS ANÆMIA

Number of patients	R.B.C. M. per c.mm.		Hb grammes %		Serum B_{12} concentration μμg./ml.	
	Range	Mean	Range	Mean	Range	Mean
9	3·9–4·3	4·1	13·1–14·4	13·9	20–95	68
3*	3·9–4·5	4·1	13·5–13·7	13·6	<20–20	<20

*These patients had subacute combined degeneration of the cord.

In 3 patients with little or no anæmia but with subacute combined degeneration of the cord (S.C.D.) the serum B_{12} concentrations were very low indeed (Table I). We have always found very low serum B_{12} concentrations in patients with this condition irrespective of the degree of their anæmia. Presumably in the patients with S.C.D. and little or no anæmia the blood count is maintained by adequate amounts of folic acid.

The changes in the serum B_{12} concentrations, blood count, and bone marrow of patients with pernicious anæmia treated with B_{12}

We have described elsewhere the way in which we have tried to correlate the changes in the B_{12} concentrations of serum and the hæmatological changes that follow treatment with B_{12} (Mollin and Ross, 1953).

After therapeutically effective intramuscular injections of B_{12} the serum B_{12} concentrations of patients with pernicious anæmia in relapse rise to within the normal range and remain elevated for a variable time depending on the size of the injection, the amount excreted, and on the individual

requirements of the patient for B_{12}. While the serum B_{12} concentrations are within the normal range the marrow remains normoblastic. When the serum B_{12} concentrations fall below about 90 to 120 µµg./ml. megaloblastic hæmopoiesis reappears in the marrow.

Similar changes follow the administration of large oral doses of B_{12} (Ross *et al.*, 1954) or smaller oral doses given with a source of intrinsic factor. Fig. 1 shows the changes in the blood count and

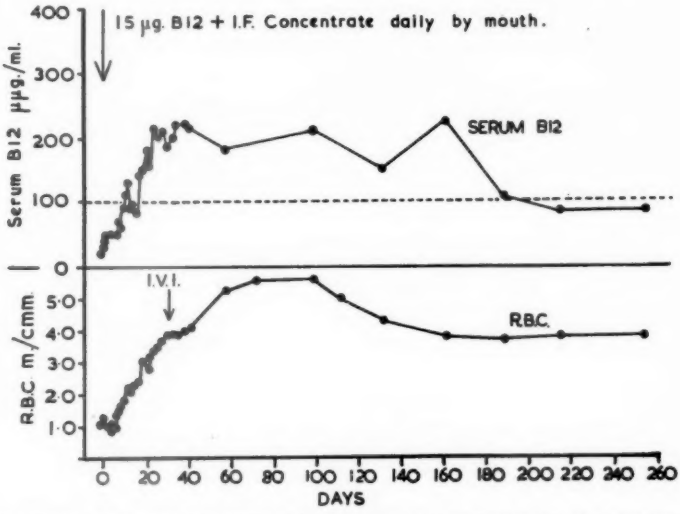

FIG. 1.—The changes in the red cell count and the serum B_{12} concentration of a patient with pernicious anæmia treated with vitamin B_{12} and intrinsic factor given daily by mouth. The broken line in the upper half of the chart represents the lower limit of the range of serum B_{12} concentrations in normal subjects.

serum B_{12} concentration of a patient who was treated with a daily dose of 15 µg. of vitamin B_{12} with a concentrate of hog's stomach containing intrinsic factor (Bifacton 2 tablets daily). The serum B_{12} concentration gradually rose and was consistently above the normal range after about twenty days of treatment. The blood count rose steadily until about the thirtieth day when signs of iron deficiency began to appear in the patient's blood. She was treated with intravenous iron and her blood count then rose to 5·0 million per c.mm. Both the serum B_{12} concentration and the blood count subsequently fell. We think this was because the patient did not take the tablets regularly, but the patient consistently denied this.

Patients with other megaloblastic anæmias.—The results of the pre-treatment serum B_{12} assays in these patients are summarized in Table II.

TABLE II.—THE PRE-TREATMENT SERUM B_{12} CONCENTRATIONS OF PATIENTS WITH VARIOUS MEGALOBLASTIC ANÆMIAS

Condition	Number of patients	Pre-treatment serum B_{12} concentration µµg./ml. Normal >100	Low <100
Pernicious anæmia	190	0	190
Total gastrectomy	4	0	4
Partial gastrectomy	9	2	7
Intestinal anastomosis; strictures	7	2	5
Idiopathic steatorrhœa	33	20	13
Non-tropical nutritional megaloblastic anæmia*	6	3	3
Megaloblastic anæmia of pregnancy	31	29	2

*The 3 patients with non-tropical nutritional megaloblastic anæmia who had low serum B_{12} concentrations were vegetarians. 2 of the other 3 patients with this condition were suffering from scurvy.

The great majority of *patients with normal pre-treatment serum B_{12} concentrations* did not respond to treatment with B_{12} but responded to treatment with folic or folinic acid. The effect of treatment

with B_{12} and folinic acid on such a patient is illustrated in Fig. 2. The patient was suffering from megaloblastic anæmia of pregnancy. She was treated first with B_{12} and then with folinic acid. There was little or no response to a single injection of 40 µg. of B_{12} or to the single very small injection of 60 µg. of folinic acid. There was a satisfactory response to treatment with larger doses of folinic acid. Presumably such patients are suffering from a pure and complete, or almost complete, deficiency of folic acid.

There are, however, a few patients with *severe* megaloblastic anæmia whose pre-treatment serum B_{12} levels are within the normal range but who yet show some response to treatment with large doses of B_{12}. The concentrations in these patients though normal are a low normal, being between 100 and 150 µµg./ml. The hæmatological responses of these patients are usually suboptimal and incomplete even when large doses of B_{12} are given and are very definitely suboptimal to doses of 20 to 40 µg. of B_{12}—doses which are capable of producing dramatic responses in patients with pure B_{12} deficiency. Dr. Badenoch has referred to one such patient. The fact that the serum B_{12} concentrations of these patients are within the normal range indicates that they are not suffering from severe B_{12} deficiency, though minor degrees of deficiency may be present. It is unlikely that the severe anæmia in these patients is due solely to B_{12} deficiency; deficiency of folic acid or failure to

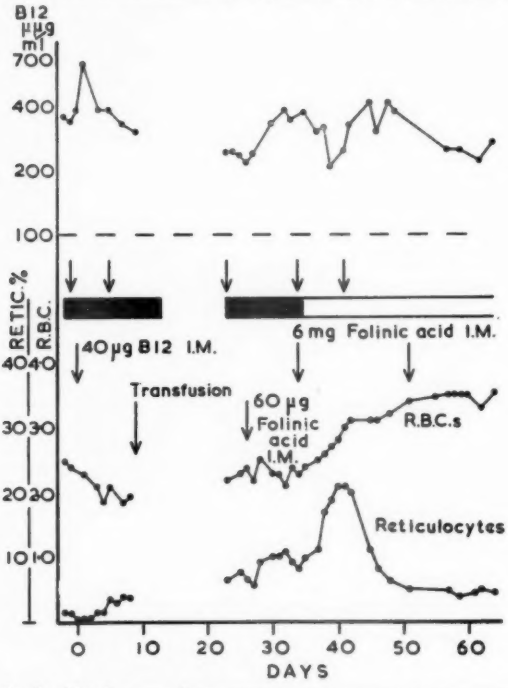

FIG. 2.—The changes in the blood count, bone marrow and serum B_{12} concentration of a patient with megaloblastic anæmia of pregnancy treated first with an injection of vitamin B_{12} and then with injections of folinic acid. The serum B_{12} concentrations are shown in the upper part of the figure. The broken line represents the lower limit of the range in normal subjects. The marrow changes are indicated diagrammatically above the blood count. The black shading indicates a megaloblastic marrow; the absence of shading a normoblastic marrow. The arrows indicate marrow punctures.

utilize folic acid must play a considerable part in the production of the anæmia. Presumably these patients cannot be completely deficient in folic acid or they would not respond to treatment with large doses of B_{12}.

The great majority of *patients with low pre-treatment serum B_{12} concentrations* respond to treatment with B_{12} as readiiy and completely as do patients with uncomplicated pernicious anæmia. In these patients the megaloblastic anæmia appears to be entirely due to deficiency of vitamin B_{12}.

However, there are a few patients with severe megaloblastic anæmia and pre-treatment serum concentrations below the normal range who respond inadequately to treatment with vitamin B_{12} alone. The concentrations may be as low as those found in pernicious anæmia of comparable severity or they may be rather higher lying between 60 and 100 µµg./ml. (an unusual finding in a

patient with a severe uncomplicated pernicious anæmia). Such patients may show an "optimal" reticulocyte response and "optimal" or almost "optimal" red cell response to single injections of 100 to 200 µg. of vitamin B_{12}. But megaloblastic change reappears in the marrows of these patients while their serum B_{12} concentrations are still within the normal range. If these patients are then treated with folic or folinic acid they will respond hæmatologically to this treatment but the serum B_{12} concentrations will gradually fall once more to low levels. This is in contrast to the results of treatment in patients with pernicious anæmia in whom the marrow does not again become megaloblastic until the serum B_{12} level has fallen below the normal range.

Conclusions

We have briefly discussed some of the ways in which the assay of the B_{12} concentrations of serum may be of value in the investigation of the megaloblastic anæmias.

The method has proved particularly valuable for demonstrating B_{12} deficiency in patients who have little or no hæmatological evidence of such deficiency. In such patients serum B_{12} concentrations of about 100 µµg./ml. or less indicate B_{12} deficiency. The method is useful for confirming the diagnosis of subacute combined degeneration of the cord in patients without anæmia; in these patients the serum B_{12} concentrations are always very low.

Because the assay of the concentration of B_{12} in the serum is more sensitive for demonstrating B_{12} deficiency than ordinary hæmatological techniques it is valuable for determining the exact incidence of B_{12} deficiency in various special populations, e.g. in patients following gastrectomy, in vegetarians or in the relatives of patients known to be suffering from pernicious anæmia. By studying such groups it should be possible to discover how long an interval may elapse before demonstrable anæmia develops after the serum B_{12} level has fallen below the normal range. In some patients with pernicious anæmia we have found the serum B_{12} level to be low but the blood picture normal or almost normal for periods of at least one to two years.

It is also a most convenient method of determining the specific deficiency in patients with florid megaloblastic anæmia and used in conjunction with the hæmatological response to treatment it can help to prove a double deficiency of B_{12} and folic acid.

Acknowledgments

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[*March* 9, 1954]

Pharmacology and Experimental Medicine [*Abridged*]

PRESIDENT'S ADDRESS

By G. A. H. Buttle, O.B.E., M.A., M.R.C.S., L.R.C.P.

It has become commonplace to refer to the enormous developments in Therapeutics. As judged by the rather crude standard of the number of new drugs introduced, there have been as many new ones since 1900 as in the whole of the previous history of the subject. Whereas fifty years ago improvements in treatment were dependent only on clinical observation of patients, recently the great majority, but not all, of the advances have come in the first instance from the results of animal experiment. The initiative has rested to a great extent with the pharmacologist and the chemist whose responsibility it had become to suggest substances for clinical trial. Of course it only too often happens that many substances which are suggested do not fulfil the hopes originally placed in them and the trial and final assessment must always be the result of years of clinical work.

These great developments are by no means all due to animal experiment and the new knowledge has so awakened interest in therapeutics that a great number of discoveries are now being made during the treatment of patients themselves. Thus, the effect of cortisone and ACTH in rheumatoid arthritis would never have been predicted but for the work on patients. This field of clinical experiment is developing fast and may lead to as rich a harvest in therapeutic discovery in the future as animal experiment has done in the immediate past.

The work of the pharmacological departments of large drug firms has done much for therapeutics. They are not troubled to the same extent with the important question of the cost of research, but they are often unwilling to grapple with problems which may require much time before any result can be expected, and the "sponsored project" to produce a new antihistamine or a new antimalarial sometimes leads to work being directed to fields where there are often already a number of available remedies more than to the difficult problems where no advances as yet have been made. However difficult and unpromising these problems may appear it is important that work be directed to their solution, for the treatment of diabetes appeared unpromising before Banting and there was very little indication of the possibility of chemotherapeutic substances for bacterial infection before the sulphonamides.

Discoveries have usually only been made possible by years of hard work but in many important advances a lucky chance and the ability to make use of it have also been very important. The use of dyes in chemotherapy has been popular since the time of Ehrlich, and Domagk was experimenting with Prontosil because the introduction of a sulphonamide group into a dye had been found to increase its fastness in staining wool fibre. As in many pharmacological discoveries the reason which prompted the choice of the substance had little to do with the way in which it was finally shown to act.

Therapy of Infections

The therapy of tuberculosis is a problem which presents many features different from those encountered in the acute infections, and there is a striking lack of correlation between the results of *in vitro* and *in vivo* tests due presumably to the inaccessibility of the organism in the infected host. The sulphone, dapsone, was the first substance to produce a significant effect in experimental infections and later streptomycin proved very much more effective. A notable advance has been made by the use of two antituberculous agents together; although one may be much less potent than the other, the use of the two together greatly delays the development of resistance to either. The sulphone, dapsone, was first combined with streptomycin, then PAS and streptomycin were found much more satisfactory, and now it seems possible that streptomycin, with its many disadvantages, may be entirely dispensed with, and that PAS and isoniazid may prove as effective as any other combination. Organisms quickly become resistant when either agent is used alone but when the two are combined the development of the resistance is very considerably delayed. It is very interesting that these principles have become more apparent as the result of clinical trials in patients when the organism is in contact with antituberculous agent for a much longer period than in animal experiments, which last only a few weeks. It would be of interest to know whether three agents together might be significantly better than two. It is very possible that further research may show more potent agents. The latest addition to this field, pyrazinamide, when combined with isoniazid was found to get rid of all the tubercle bacilli in mouse spleens more readily than any combination previously tried, and results on patients have been equally promising except for occasional appearances of liver damage.

The treatment of leprosy is a problem somewhat clearly associated with that of tuberculosis. The sulphone, dapsone, was soon found to be effective, but both streptomycin and isoniazid when given alone do not have an appreciable effect. Although dapsone and its derivative, solapsone, have proved far more reliable than any other means of treatment so far employed, the response is extremely slow and in a series of cases examined six months after the inception of treatment and compared with an equal number of controls, only 30% more of the treated cases were noted as improved in comparison with the controls. In the assessment of new drugs it is not possible to use *in vitro* methods or to test on infected animals. The clinical test is so slow that eighteen months elapses before a result is available, also large quantities of material are required for the trials. There is so much clinical material available that it is regrettable that more trials of new drugs are not being carried out, and, in particular, it would seem worth trying combinations which have proved so effective in tuberculosis.

The many substances which are now available for the treatment of bacterial diseases, a development started by the discovery of the sulphonamides, have rendered possible the treatment of all infectious conditions except those with pathogenic fungi at one end of the scale, and those with the smaller viruses at the other end. Amongst the pathogenic fungi actinomycosis responds to penicillin, and much active work is in progress to find agents which will deal with the others. The large viruses, lymphogranuloma and psittacosis, respond to the same general lines of chemotherapy as do bacteria. The small viruses on the other hand seem to present an entirely different problem. Both influenza and poliomyelitis have so far completely eluded all attempts at chemotherapy.

The problem of the chemotherapy of virus infections is very much more difficult than that of bacterial infections. The virus is a more intimate part of the cell of the host. The rate of multiplication of the virus is far greater than that of the bacteria and our difficulty is considerably increased by our inability to grow the virus apart from the animal tissue. The introduction of tissue culture work may prove a considerable help in this matter, but so far no very significant advances have been made.

A number of very different substances are found to have a possible small influence on the rate of multiplication of the poliomyelitis virus in the mouse, but none of these have been sufficiently active to suggest any line of further investigation.

So far it appears that there is no suggestion of the possibility of influencing the virus once the infection is established although there are indications of the possibility of the inhibition of one virus by another and of the inhibition of some neurotropic virus infections by the use of dyes, notably trypan red. These effects have, however, not been of such a character as to make possible a therapeutic test in man.

The only possible means of protecting against the infections with the smaller viruses at the moment is by active immunization, and it appears that the field of the chemotherapy of viruses is one which may require a great deal of work before any significant advance can be achieved.

Therapy of Cancer

The treatment of cancer still presents a most difficult and unpromising problem for the pharmacologist. This is an important question now, and is likely to become a much more urgent one in the future owing to the successful therapy of nearly all infectious conditions. The main attempts at treatment other than by surgery or by irradiation have been by hormones and by excision of endocrine glands, by substances which inhibit cell division, such as nitrogen mustard, and by substances which may interfere with the utilization of metabolites such as aminopterin, and 6-mercaptopurine. Nitrogen mustard, or mustine, has been found useful in Hodgkin's disease and its action appears to depend on the formation of a cross linkage between the chromosomes of the dividing cells. Other derivatives which have been developed from it are T.E.M., also used in Hodgkin's disease, Myleran used for chronic myelogenous leukæmia and bischloroethylaminophenyl butyric acid for chronic lymphatic leukæmia. In the case of all the substances resistance to the drug soon appears.

This development of resistance is a phenomenon which is also marked in the therapy of tuberculosis, and in the latter case the most useful approach to the problem has been through the use of two antituberculous agents together, presumably the one can deal with the bacteria which have become resistant to the other. It would be interesting to determine whether any effect of the same character could be observed in the treatment of cancer. Although the pathological conditions are absolutely different, the rapidly dividing cancer cell may possibly be induced to behave in a manner analogous with that of the tubercle bacillus in this respect. In connexion with this it would be of particular interest if another drug in addition to nitrogen mustard could be found to influence Hodgkin's disease. Possibly if such were found a much better effect might be produced than that found with nitrogen mustard alone. There appears to be some evidence for the advantage of combined treatment in acute leukæmias and the use of aminopterin and 6-mercaptopurine together in cases of acute leukæmia has given a better result than either agent alone.

Hormone treatment of breast and prostate tumours is common practice and ovariectomy was first tried for inoperable breast tumours by Sir George Beatson in 1869, but it did not give consistent effects. It has been known for a long time that in pathological conditions the adrenals can produce steroids with œstrogenic and androgenic functions and recently Huggins appears to have made a considerable advance in the treatment of inoperable differentiated breast tumours by performing bilateral adrenalectomy in patients without ovarian function; and maintaining them by injections of DOCA and cortisone.

The development of resistance to nitrogen mustard and similar substances is an interesting point of study with transplantable tumours like the Walker rat tumour where resistance once it is established is maintained during any number of further transplantations. Such research may eventually show some indication for improving the effect of the drug in Hodgkin's disease.

General

One of the aspects of pharmacology to which a great deal of attention is now being directed is the production of inhibitory drugs. These may be either drugs which inhibit the action of a substance occurring in the body, like adrenaline, histamine or acetylcholine, or they may be drugs which are thought to act by so-called substrate competition and prevent the access to an invading organism of some necessary metabolite, as in the case of sulphanilamide and para-aminobenzoic acid. Inhibitory drugs sometimes have a structure very similar to that of the substance whose action they are inhibiting, thus nalorphine has a structure identical to that of morphine except for the substitution of the methyl by the allyl group; on the other hand sometimes, as in the case of the antihistamines, although the original drugs closely resembled the substance to be inhibited, further modifications have almost completely obliterated the resemblance. In the production of inhibitory substances to known drugs, chemical modifications of the molecule as by the introduction of an unsaturated group in the case of nalorphine, or by alteration in the distance between polar groups as in the methonium series, does give a guide to the design of the inhibitor, at any rate in the initial stages of the work. In chemo-

therapy such theoretical considerations have not led to practically useful results, the explanation of the action, if it is discovered at all, usually only follows at a long interval after the drug is found.

Chemotherapy has remained a science where a number of substances must be tried in the whole animal, and there are comparatively few rules to indicate to the experimenter the best road to follow. The one exception to this is the finding of Hawking and MacIlwain that pantoyltaurin would prevent the assimilation of pantoylthenate by hæmolytic streptococci and thus act as a chemotherapeutic agent in infections of the rat but not in the mouse. This work has no practical usefulness at present, but may well be a pointer as to the design of experiments for the future. It seems that we must wait for further considerable developments in biochemistry before chemotherapy can become in any way an exact science.

Several discoveries in therapeutics have come from observations on patients alone. Thus the action of digitalis on the heart in auricular fibrillation and later that of quinidine, would never have been found but for clinical observation. In the case of liquid extract of ergot, the pharmacologists were sceptical of the action on the uterus observed by gynæcologists, as laboratory experiments gave no indication of its activity, and it contained no ergotoxine or ergotamine. The discovery of ergometrine in this liquid extract depended entirely on the observations in the human patient, and this finding was made by a clinician so sure of his observations on his patients that he continued his work in spite of some discouragement from those who had worked only on animals.

The discovery of the action of cortisone and of ACTH in rheumatoid arthritis was suggested by the observation of the remissions of the condition in pregnancy and jaundice, conditions where the suprarenal cortex was known to be more active than usual. Although this discovery has stimulated a great deal of experimental work on animals, the initial step was entirely due to clinical observation.

Recently the action of phenylbutazone in rheumatoid conditions was observed owing to the substance being used as a solvent for amidopyrine.

It would seem that an ever-increasing number of discoveries may well be made by observations on patients in the future, particularly as clinicians become more interested in the action of the drugs they use. In so many conditions it is not possible to imitate the disease on the experimental animal, and it is here that clinical pharmacology is of paramount importance. There is certainly need in pharmacology to tackle problems which are of use to clinicians, and probably an even greater need for clinicians to cultivate an interest in pharmacology and to observe and investigate any unusual effects seen in their patients.

Section of Endocrinology

President—RAYMOND GREENE, M.A., D.M., M.R.C.P.

[*November* 25, 1953—*continued*]

Bilateral Ovarian Hernia.—P. F. HALL, M.R.C.P., and P. M. F. BISHOP, D.M., M.R.C.P.

V. H., aged 8 months, was brought to the Surgical Out-patients of Guy's Hospital, the mother having noticed a lump in each groin. The child was referred to Dr. P. M. F. Bishop who considered that in all probability the lumps were testes and that the child was a male pseudohermaphrodite.

On examination.—A lively child with normal female genitalia. There was a lump present in each groin about ½ in. in diameter, oval in shape, firm, non-tender and mobile.

Family history.—Nothing of this sort was known to have occurred on either side of the family.

Previous diseases.—Nil.

Investigations.—Hæmoglobin 78%, W.B.C. 7,800 per c.mm., R.B.C. 4,100,000 per c.mm.

Chest X-ray: Normal.

Operation 8.10.53 (Mr. Nils Eckhoff).—Biopsy was taken from each gland.

Histology.—Ovary showing many Graafian follicles and a few simple follicular cysts (see Fig. 1).

It was decided that replacement of the ovaries into the cavity could be performed then and there; this was easily accomplished and the ovaries, which were in the canal of Nuck, were slipped back into the abdomen and the hernial sac was excised and the wound closed.

This case was considered to be of special interest because of its rarity.

It is puzzling to imagine how an ovary and fallopian tube could appear in either groin unless it be that the uterus is bicornate or in some way grossly deformed. Laparotomy was not considered justifiable.

FIG. 1.—Photomicrograph of biopsy taken at operation, showing normal immature ovary.

Addison's Disease Presenting as Psychosis.—ARNOLD BLOOM, M.D., M.R.C.P.

Mrs. L. S., aged 49, housewife.

History.—Summer 1950: exposed skin unusually tanned, especially the neck. Pigmentation persisted during winter and subsequently. Spring 1952: easily tired and bouts of vomiting. Began to show difficulty in grasping conversation, patchy loss of memory with increasing disorientation and delusions. Admitted to mental hospital in December 1952 in manic state. Slow improvement and discharged after six weeks. April: bouts of nausea and vomiting with nose bleeds, asthenia and dizziness, followed by disorientation, incomprehensible speech and restlessness. 25.4.53: Again admitted and transferred to Neuro-Surgical Unit, Whittington Hospital, as suspected subdural hæmatoma.

Previous history.—Hysterectomy for fibroids April 1948.

On admission.—Thin woman, drowsy, confused and collapsed. Brown pigmentation on exposed skin and inside mouth. Absent axillary hair, scanty pubic. Extremities cold, pulse slow, poor volume. B.P. 95/60. No localizing C.N.S. signs.

Treatment.—Intravenous saline glucose, with Eucortone : intramuscular cortisone. Later DOCA by injection and salt and cortisone by mouth.

Investigations.—Sodium 250, potassium 20·5, urea 40, blood sugar 80 mg.%, normal glucose tolerance curve. B.M.R.—24%. 17-ketosteroids 2 mg./24 hours. Cholesterol 171 mg.%. R.P.K. test: night urine 560, largest day 70 ml.; A = 4. C.S.F. normal. W.R. negative. Hb 89%, W.B.C.

2,800 (46% polys.). Cerebral arteriogram and X-ray chest: normal. X-ray abdomen: no calcification. ECG: sinus bradycardia, low voltage, flattened T waves.

Progress.—Since July 1953, salt and cortisone (37·5 mg. daily) by mouth only. Steady physical and mental restoration, does full day's work, feels well. Pigmentation less marked, pubic hair increased. B.P. 100/75. Sodium 330 mg.%. ECG: T waves upright.

Comment.—While mental disturbances, such as apathy, negativism, depression and irritability, are not unusual in Addison's disease, frank psychoses are rare. Hitherto, treatment has been of doubtful value in this direction and it remains to be seen if cortisone offers a better prognosis.

My acknowledgments are due to Doctors A. L. Jacobs, K. Robinson and A. Hunter.

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[*January* 27, 1954]

DISCUSSION ON MALE HYPOGONADISM

Dr. G. I. M. Swyer, University College Hospital: *Male Hypogonadal Syndromes*

The two functions of the testis are to produce hormones and to produce spermatozoa. It is logical, therefore, to include under the heading "hypogonadism" insufficiency of either of these functions. In general, however, the term is confined to insufficiency of endocrine activity and it will be my plan to restrict attention mainly to this aspect of the subject. Nevertheless, an exception will be made in the case of a syndrome in which gametogenesis is the only deficient function because this particular condition helps to throw some light on testicular physiology.

As the clinical features of eunuchoidism in its various forms are generally well known, I shall briefly describe only the structural state of the testis and the hormonal aberrations as found in the various hypogonadal syndromes.

It is logical and convenient to consider two main forms of hypogonadism, namely, *primary* where the main lesion resides within the testis itself and *secondary* where testicular changes are due to deficiency of pituitary gonadotrophic stimulation. Before puberty, a condition of physiological hypogonadism exists because there is little or no production of gonadotrophins by the pituitary gland. When, at puberty, the pituitary gland becomes functionally effective, over-secretion of gonadotrophin arises where the testis is unable to respond, so that in primary hypogonadal states an excessive urinary excretion of gonadotrophin is a diagnostic feature. In secondary hypogonadism, however, the excretion of gonadotrophin is very low. It follows, therefore, that determination of the urinary gonadotrophin level is a key diagnostic test in differentiating these two kinds of hypogonadism. But since the existing methods of gonadotrophin assay are crude in the extreme, it is not surprising that doubtful cases are sometimes encountered.

Primary hypogonadism.—This can be either congenital or acquired. Congenital primary male hypogonadism is grouped by Sohval and Soffer (1953) as follows: (1) anorchism (testicular agenesis), (2) prenatal testicular atrophy, (3) germinal aplasia (testicular dysgenesis), (4) failure of normal differentiation of Leydig cells (testicular dysgenesis) due to (*a*) long-standing cryptorchidism or (*b*) unknown causes, (5) as part of syndromes or diseases characterized by multiple congenital anomalies, including (*a*) Laurence-Moon-Biedl syndrome (certain cases), (*b*) dystrophia myotonica, (*c*) male counterpart of Turner's syndrome, (6) non-classifiable because of inadequate clinical, histological or hormonal data.

Bilateral anorchism is exceedingly rare, though the unilateral variety is probably less uncommon. The first authentic case of bilateral anorchism was recorded in 1564 (quoted by Sohval and Soffer, 1953). This occurred in a soldier who was hanged for rape and in whom post-mortem examination failed to disclose testes in the scrotum or abdomen. Prenatal testicular atrophy may be very difficult to differentiate from true testicular agenesis.

The term germinal aplasia was first introduced by Engle in 1947. He considers, as do del Castillo *et al.* (1947), that this condition, in which there is complete absence of cells of the spermatogenic series, though Sertoli and Leydig cells appear to be intact, is congenital in origin. It is suggested that there is a failure of migration of the primordial germ cells during embryonic life from the yolk sac endoderm to the median cell ridge. The gonadotrophin excretion in these patients may be entirely normal, though in some instances it appears to be elevated. A condition in which the testicular biopsy is indistinguishable from that described above may arise where normal testes have been exposed to irradiation.

The other form of testicular dysgenesis is that in which the Leydig cells are not normally differentiated. McCullagh *et al.* (1953) have recently drawn attention to "A syndrome of eunuchoidism with

spermatogenesis, normal urinary FSH and low or normal ICSH ('fertile eunuchs')". In 2 of their 5 patients the ICSH (or LH) excretion was normal, yet Leydig cells were apparently absent. In the other 3 patients, the ICSH excretion appeared to be low, so that these patients should therefore be regarded as examples of secondary hypogonadism. It is interesting to note that sperm counts in these patients ranged from very low figures (though not azoospermia) to 102 millions per ml. Landau (1953) has described a similar case of hypogonadism with spermatogenesis; this man had mild hypogonadism and unusually low seminal fructose. Androgen treatment led to a rise in the seminal fructose, the completion of masculinization and a temporary increase in the output of spermatozoa.

The hypogonadism of the Laurence-Moon-Biedl syndrome has generally been assumed to be secondary to pituitary gonadotrophic deficiency. Roth (1947) was the first to prove this by urinary gonadotrophin assays. More recently, Francke (1950) has shown that in some of these patients gonadotrophin production is probably not deficient. In a 45-year-old patient who came to necropsy the testicular condition was indistinguishable from that found in the Klinefelter syndrome. It is probable, therefore, that in some at least of the cases of Laurence-Moon-Biedl syndrome, the hypogonadism is primary, the gonadal defect being just one more of the multiple congenital anomalies.

The association of gonadal deficiency with dystrophia myotonica has been known for a long time. A number of recent reports (Nadler *et al.*, 1950; Howard *et al.*, 1950; Benda and Bixby, 1947) have described the testicular lesions in this condition: complete tubular sclerosis with normal Leydig cells and no interstitial fibrosis appears to be the rule. The urinary 17-ketosteroids are usually low and the gonadotrophins usually, though not always, elevated.

It would seem that Turner's syndrome in the male forms a less well-defined entity than when found in the female (Sohval and Soffer, 1953; Prunty *et al.*, 1953). The combination of deficient stature, congenital anomalies of various kinds, testicular hypoplasia with androgen deficiency and increased urinary gonadotrophins would qualify a male for inclusion in this category. Of the various cases described in the literature, no uniformity of testicular pathology has been found. This is in contrast to the condition in the female, where the ovaries consist merely of stromal elements with associated structures, such as rete and medullary canals, but with total absence of the follicle apparatus. The above remarks on the heterogeneity of male Turner's syndrome apply also to a variety of miscellaneous cases of congenital primary hypogonadism in which mixed testicular lesions are found. Two such cases occurring in brothers are reported by Sohval and Soffer (1953). These men had a moderate degree of androgen deficiency, small testes, aspermatogenesis, gynæcomastia and increased urinary gonadotrophins. The testicular lesions differed from those of the Klinefelter syndrome; there was germinal aplasia, together with a varying extent of completely hyalinized tubules.

Acquired primary hypogonadism includes the following main conditions: (1) surgical castration; (2) functional pre-puberal castration (some cases); (3) Klinefelter-Reifenstein-Albright syndrome (sclerosing tubular degeneration); (4) mumps orchitis; and (5) male climacteric.

The first of the above conditions requires no special comment. Functional pre-puberal castration was first described by Heller, Nelson and Roth (1943). Some of their cases probably fell into the congenital group, but in others the lesion was very likely an acquired one. The testes are found to be absent or completely atrophic, though characteristically the Wolffian duct derivatives descend into the scrotum. It is probable that many of these patients are mistakenly labelled as cryptorchid. Gynæcomastia is common.

The syndrome of sclerosing tubular degeneration was first described by Klinefelter, Reifenstein and Albright in 1942 as a "Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism and increased excretion of follicle-stimulating hormone". It has since been the subject of numerous further reports. The condition has its onset at about the time of puberty, either earlier or later, and involves fibrosis and hyalinization of the basement membrane of the seminiferous tubules, thereby leading to the cutting off of the blood supply to the tubular contents. There is, in consequence, a greater or lesser degree of destruction of the entire tubular contents—germinal epithelium and Sertoli cells. In addition, the Leydig cells may be affected to varying degrees; in many cases they appear to be increased in numbers, and, by the use of special staining techniques, it can be shown that they are morphologically abnormal.

Heller and Nelson (1945) subdivided these patients into three groups: (1) eunuchoidal, (2) moderately eunuchoidal, and (3) non-eunuchoidal. This grouping depends upon the degree of failure of Leydig-cell function. In general, the extent of gynæcomastia appears to be related inversely to the degree of Leydig-cell failure, so that it is greatest in the least eunuchoidal types. There are, however, exceptions to this general rule.

Bilateral mumps orchitis may produce a condition essentially similar to the Klinefelter syndrome just described above. The extent of sclerosis, however, is usually more variable, and there is, commonly, a great deal of interstitial collagenous tissue. The Leydig cells may be quite normal. The urinary gonadotrophins are elevated, and the 17-ketosteroids are either normal or reduced.

Concerning the male climacteric, Heller and Myers (1944) state: "Whereas in the female the menopause is an invariable and physiologic accompaniment of the ageing process, in the male the climacteric is an infrequent and pathologic accompaniment of the ageing process." In authentic

examples of the male climacteric, the output of gonadotrophins is increased, indicating primary testicular failure. Howard *et al.* (1950) describe 6 such cases and in all of them the testicular biopsy showed no abnormality. They therefore considered that these patients were still in the "compensated" stage.

Secondary hypogonadism.—As previously mentioned, the normal pre-puberal child displays secondary hypogonadism but requires no further notice here. In pituitary dwarfism, there is, presumably, a failure of all the trophic functions of the anterior lobe of the pituitary gland. The testes, along with the other target endocrine glands, remain in an unstimulated condition. The commonest variety of eunuchoidism is that due to idiopathic deficiency of follicle-stimulating hormone (FSH) production by the pituitary gland. Gynæcomastia rarely occurs in this condition. The 17-ketosteroid excretion ranges between levels such as would be found in pre-puberal boys to low adult figures. The FSH excretion is, of course, low. The testicular histology is very similar to that found in the pre-puberal state.

The presence of an organic lesion in or near the pituitary gland may lead to insufficiency of gonadotrophin production, and so to secondary hypogonadism. The testicular lesion appears then to depend on the stage of testicular development attained prior to the onset of gonadotrophin suppression. When this happens before the completion of testicular maturity, the general appearance is similar to that in idiopathic eunuchoidism, except that the tunica propria of the tubules is found to be thickened. When the lesion is of later onset, more extensive degenerative change is usually found. Again, thickening of the tunica propria occurs, but in these cases is very marked, accompanied by peritubular fibrous tissue proliferation and Leydig-cell degeneration. There is extensive impairment of germ-cell activity and the Sertoli cells contain lipoid-filled vacuoles.

Hypogonadism without endocrine disturbance.—In this group the main complaint is usually of infertility which may range from azoospermia to varying degrees of oligospermia. Azoospermia due to duct obstruction is, of course, excluded. The three main varieties are (1) germinal aplasia, which has been mentioned already; (2) arrest of maturation; and (3) hypospermatogenesis. Little or nothing is known of the causes of these two latter conditions which, by the definition of this group, would appear not to be of endocrine origin.

Pituitary-testicular interrelationships.—The finding of increased outputs of pituitary gonadotrophin in primary hypogonadism calls for further consideration. In the case of the female, no difficulty is encountered in providing an explanation: the failure of the ovary to secrete œstrogen leaves the pituitary unimpeded by the inhibiting effect which this steroid has on its gonadotrophin production, and so the gonadotrophin output is increased, with the accompaniment of characteristic histological changes, namely the appearance of the so-called castration cells. In the male, however, gonadotrophin excretion may be increased, although androgen excretion appears to be unimpaired. Moreover, it is well known that the amount of androgen required to maintain the weight of the prostate and seminal vesicles in castrated rats is insufficient to prevent the appearance of castration cells in the pituitary gland. It has, therefore, seemed reasonable to suppose that a second testicular hormone might be produced, having as one of its effects the ability to inhibit the over-production of pituitary gonadotrophin. This view has been elaborated by Howard *et al.* (1950) who term the second hormone "X hormone", thereby implying that its nature is not known. They prefer this description to the older name "inhibin" introduced by McCullagh (1932), since this latter is supposed to be a water-soluble substance. They advance several reasons for supposing that X hormone is produced by the Sertoli cells. Most important, perhaps, is the fact that this substance would appear to be absent when the Sertoli cells are absent or markedly reduced in numbers (for example, as in the Klinefelter syndrome), whereas in germinal aplasia, where the Sertoli cells are apparently unaffected, FSH excretion may be normal, suggesting that X hormone is present in normal amounts. As further actions of the X hormone, it is considered that it stimulates the production of luteinizing hormone, or possibly luteotrophin, by the pituitary gland and inhibits the development of gynæcomastia.

An alternative explanation of the high FSH excretion in primary hypogonadism is advanced by Heller, Heller and Sevringhaus (1942). According to their view, the rise in FSH excretion in both menopausal and ovariectomized women is due to a failure of the ovaries to remove FSH from the blood. The same reasoning has been carried over to males, the increased FSH excretion there being attributed to failure of the seminiferous tubules to utilize the hormone. Such an interpretation fails to explain the increased gonadotrophin content of the pituitary gland of castrated animals and it rather implies that most of the blood must pass through the gonads before it reaches the kidneys. Most important of all, however, it completely fails to explain the decreased FSH output following œstrogen administration.

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Dr. D. G. Ferriman, North Middlesex Hospital: *Familial Hypogonadism*

Hereditary transmission of hypogonadism seems unlikely, but undoubtedly does occur, and a little reflection shows how this may come about. Recessive and sex-linked forms present no difficulty, but dominant transmission calls for some explanation. Any hereditary disorder manifests itself in very varying degree from forms which may evade clinical detection to the grossest of abnormalities. There is no reason to suppose that an all-or-none law applies to hypogonadism any more than to other hereditary disorders. Lightly affected individuals may therefore be potentially fertile, if relatively less so than normal people. This is an important principle and perusal of the literature shows it to be true.

Determination of the primary seat of the disorder—whether pituitary or gonadal—is helpful in classifying the various types of hypogonadism but the distinction is perhaps not as easy as it seems at first sight. The distinction is made on the results of FSH estimations, testicular biopsies, and treatment with gonadotrophins.

While high FSH excretions are thought to be indicative of primarily gonadal failure, low or normal excretions may not necessarily indicate a pituitary origin. For example, if a primary gonadal lesion spared the cells responsible for inhibiting gonadotrophin production, the FSH excretion might not be raised.

Tubular sclerosis is a feature of primary testicular lesions. If a primarily pituitary failure is delayed, however, until after the onset of puberty, tubular maturation may first occur, to be followed by sclerosis when pituitary stimulation fails.

An unequivocal response to gonadotrophin therapy is at present thought to be diagnostic of primary pituitary failure.

Familial Syndromes

Hypogonadal families may be classified under six main headings—dystrophia myotonica, the Laurence-Moon-Biedl syndrome, Turner's syndrome, the undescended testicle, Reifenstein's syndrome and miscellaneous.

Dystrophia myotonica.—This condition is characterized by a typical slowness in muscular relaxation, hypogonadism and frontal baldness. It is inherited in a dominant manner, and affects both males and females. FSH studies have shown the gonadal disorder to be primarily gonadal in origin. The cataract shows the phenomenon of anticipation; that is to say it appears at an increasingly earlier age in succeeding generations. The hypogonadism is not always present, and is said to appear commonly some years after the outset of puberty.

Laurence-Moon-Biedl syndrome.—This condition is characterized by retinitis pigmentosa, polydactyly, mental retardation, obesity and hypogonadism. It is inherited as a recessive and is manifest in both sexes. There is some doubt as to whether the condition is primarily pituitary or gonadal in origin. FSH excretions were low in 4 hypogonadal brothers reported by Roth (1947); gross tubular sclerosis was present, however, as in another patient reported by Francke (1950), and one brother failed to respond to gonadotrophins, though all responded well to testosterone. Of 2 female patients reported by Francke, one had high, and the other normal FSH excretions. A marked hyperplasia of basophil cells has been seen in the pituitary at two autopsies (Griffiths, 1938, and Anderson, 1941) suggesting a lack of gonadal restraint. The balance of evidence possibly favours a primarily gonadal origin at present. According to Sorsby *et al.* (1939) every single one of the components of the syndrome has been missing on occasion. Hypogonadism has been absent in a number of patients. The supernumerary digit may be absent, or—interestingly—be represented by a mere nodule.

Turner's syndrome.—FSH excretion studies indicate a primarily gonadal origin. The classical picture of a dwarfed, sexually infantile girl with a webbed neck, cubitus valgus and rudimentary ovaries probably needs some enlargement. Claims have been made for the existence of male cases, and cases with normal stature, absence of webbing, or webbing elsewhere than in the neck, and various skeletal anomalies. A curious œdema of the hands and feet has been reported in infants with the disease.

The reported male patients have possessed testicles with definite if degenerate seminiferous tubules and Leydig cells, and claims have been made for female patients with some functioning ovarian tissue. Acceptance of such cases need present no theoretical difficulty. As most of the anomalous cases have been sporadic, it is difficult, however, to be certain of the diagnosis. Study of the relatives of patients with unequivocal signs of the disorder may throw light on these and other matters. The evidence so far is scanty.

Frawley (1925) described two sisters with webbing of the neck, dwarfism and apparent absence of certain cervical vertebræ; axillary webbing was present in one sister. No pubertal development had occurred in either, though, as the elder girl was only 12, this is of doubtful significance. Rossi and Howald (1947) described a girl of 15½ with webbing of the neck, dwarfism and sexual infantilism. A cousin, of unspecified sex, suffered from webbing of the neck. Sohval and Soffer (1953) described two hypogonadal brothers. One was 68 in. in height, but the other was 5 in. smaller, had a short neck with anomalies of the cervical vertebræ and cubitus valgus.

Dr. I. G. Wickes has kindly asked me to join with him in the investigation of another family. Our quest has not proceeded very far as yet, but there are suggestive features in several members. The 3 most important members are a small girl aged 2, her mother and a second cousin. The girl was originally seen by Dr. Wickes at the age of 3 months when she presented with œdema of the hands and feet which has disappeared slowly while under observation. She is abnormally small and has a webbed neck. The mother has been seen and appears to be perfectly normal except for possible dwarfism. The second cousin, a woman aged 22, has not been seen, but is said to have the external appearances of a girl of 11 with no breast development, and absent menstruation.

The evidence is too scanty for definite conclusions, but would be consistent with a dominant heredity, affecting both males and females, of low expressivity especially in the male. The mother of Dr. Wickes' patient is of particular interest in this connexion. On a dominant hypothesis, she must be affected yet shows little or no evidence of the disorder.

The interesting family reported by Perkins in 1933, five years before Turner's original article, should be noted at this point, because it shows the same features of a dominant heredity, predilection for the female, and relatively poor expressivity. Neither dwarfism nor webbing was reported in any member, but 2 women in the first generation and 3 in the third were frankly hypogonadal. Transmission was through two lightly affected women. The first presented only scanty pubic and axillary hair; the onset of puberty was delayed in the second till the age of 17, and body hair growth was always scanty.

The undescended testicle.—The ætiology of this condition, apart from those cases with anatomical abnormalities, is obscure and may well be multiple. An hereditary factor has been demonstrated. The disorder has been reported in brothers by Wangensteen (1932), Brosius (1935), Simpson (1946), Brimblecombe (1946), Glass (1946) and Bishop (1945). It has also been reported in an uncle and nephew by Bishop (1945), and in cousins by Bishop (1945) and by Bauer (1937). Bishop (1945) has suggested a dominant mode of inheritance with somewhat low expressivity.

A degree of hypogonadism is sometimes present, and may conceivably be primary rather than secondary. McCullagh *et al.* (1953) have recently reported a small series of men with hypogonadism, low sperm counts, and testicular biopsies showing normal seminiferous tubules but infrequent interstitial cells. FSH excretions were normal but ICSH excretions were low and the patients responded to treatment by chorionic gonadotrophins with development of secondary sex characteristics and the appearance of normal sperm counts. One of these patients had a frankly hypogonadal brother (McCullagh, 1948) who also suffered from unilateral cryptorchidism. Landau (1953) has described another case of unilateral cryptorchidism with somewhat similar biopsy findings. The well known efficacy of chorionic gonadotrophins in the treatment of cryptorchidism may therefore be of ætiological significance. It is conceivable that some cases of cryptorchidism may be due to an impaired secretion of ICSH.

Reifenstein's syndrome.—A dominant sex-linked mode of inheritance seems to characterize three hypogonadal families described by Reifenstein (1947, 1948) and Kallman *et al.* (1944). They may represent a separate disease entity and the high FSH excretion in Reifenstein's patients would indicate a primarily gonadal origin for the group. There were no associated lesions apart from gynæcomastia.

Miscellaneous.—Two brothers have been observed by the author suffering from gynæcomastia, mild hypospadias, lack of beard growth, a feminine distribution of pubic hair and a diffident manner. They were rather undersized compared with other members of the family. Testicles were superficially normal, if small. FSH excretions (Dr. G. I. M. Swyer) were rather low, suggesting a primarily pituitary lesion. The parents were related (Fig. 1), suggestive of a recessive mode of inheritance. The elder brother has been reported previously (Ferriman, 1950).

The family relationships of an uncle (Sa.), Aunt (H.) and nephew (B.) studied by the author, are shown in Fig. 2. FSH excretions (Dr. G. I. M. Swyer) were low, suggesting a primary pituitary lesion. They showed varying degrees of gigantism, acromegalic appearances and hypogonadism. Skull X-rays showed no enlargement of the sella turcica. The condition might be explained by hereditary hyperplasia of eosinophil cells in the pituitary, with hypoplasia of the basophil cells. The uncle has

died recently, and examination of the pituitary seems to bear this out (Dr. J. T. Prendivalle). The condition is apparently a dominant. The nephew's father who is presumably affected has, nevertheless, produced two children.

Another family with normal FSH excretion was reported by Hubble (1951). A hypogonadal

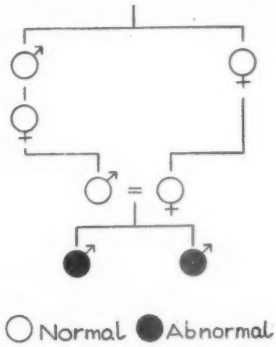

FIG. 1.—Family tree. Two brothers with gynæcomastia.

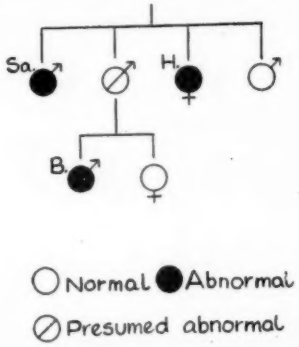

FIG. 2.—Family tree. Association of acromegaly and hypogonadism.

man aged 20, of normal stature, had a cousin, aged 8, who was a dwarf. The condition was presumed to be a primary disturbance of the pituitary gland.

It is possible that associated disturbances of other pituitary hormones may prove a distinguishing feature of hypogonadotrophic syndromes in general. The adipose gynandrism sometimes associated with undescended testicles may be a case in point.

Two other families reported by Yates (1924), that of 2 sisters, and Hurxthal (1943), that of 3 brothers, are unclassifiable.

Anorchism—complete absence of both testicles—has been reported by Koopman and delayed maturation of spermatozoa by Howard and co-workers (1950), both in brothers. This is of doubtful ætiological significance. As hereditary traits may be transmitted in varying degree, the two conditions may no more than represent extreme forms of several disorders.

IMPORTANCE OF FAMILIAL HYPOGONADISM

Most cases of hypogonadism occur sporadically, and present a bewildering variety of clinical pictures. It is difficult to decide whether the various clinical pictures represent separate diseases, or a lesser number of disorders in a variety of guises. Much the same thing applies to testicular biopsy patterns.

The study of hypogonadal families should prove a useful weapon in exploring some of these problems.

The examination of relatives of unequivocal sufferers from particular disorders should show, on the one hand, the range of manifestations in each disorder, and the overlap between them, and, on the other, those changes which are pathognomonic of each disorder.

The establishment of specific modes of inheritance may also help to distinguish the various disease entities involved.

Accurate diagnosis is not an entirely academic matter, as it underlies rational therapy and prognosis, both as to the prospects of treatment and the likelihood of transmission.

I wish to thank Professor L. S. Penrose for assistance over the genetic aspects of this paper, and Dr. G. I. M. Swyer for much help and encouragement.

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Dr. H. S. Le Marquand, Reading: *Congenital Hypogonadotrophic Hypogonadism in Five Members of a Family, Three Brothers and Two Sisters*

The father and mother of this interesting family are said to be normal and are not related. They had 6 children, 4 males and 2 females. Of these 3 males and 2 females are hypogonadal. The other brother, the youngest, is said to be normal. These patients are examples of hypogonadotrophic hypo-

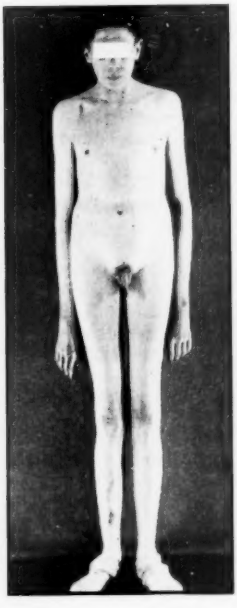

Fig. 1.

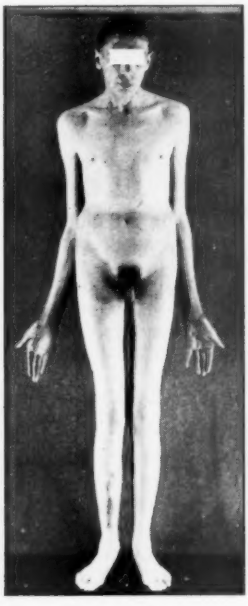

Fig. 2.

FIG. 1.—*Case* I, M., 34 yr., single. 19.1.53. Before treatment. Ht. 71 in. L.M. 41¾ in. U.M. 29¼ in. Diff. 12½ in. Span 80 in. 17-K. 2·6 mg./24 hr. Ep. age about 17 yr. Cholesterol 185 mg.%. Testes minute. Voice unbroken. No axillary hair. Gonadotrophin low.

FIG. 2.—*Case* I, 27.8.53. After treatment. Chorionic gonadotrophin 67,000 units. Methyl testosterone 900 mg. Thyroid gland grain i daily.

FIG. 9.—Case I, Section of testis.

gonadism for the following reasons: the men responded overwhelmingly to chorionic gonadotrophin; the gonadotrophin assays of the urine are less than 5 mouse units in each case and the testicular biopsies suggest pituitary rather than testicular origin.

All the patients show eunuchoid characteristics, the lower measurement is at least 8 in. longer than the upper measurement and the span exceeds the height considerably in every case. The patients have a hairless and wrinkled skin of sallow colour. Primary and secondary sexual characteristics

are very deficient; in the men the voices are unbroken, they do not shave and muscular development is poor. Epiphyseal development is very retarded, in 4 patients it corresponds to the age of 17 years. Gynæcomastia is not present. Kahn reaction of the blood serum is negative in every patient. All patients had thyroid gland (dry) 30 mg. to 60 mg. daily as an additional treatment.

The following descriptions of the patients are abbreviated and should be read in conjunction with the above paragraphs and with the information given below the figures.

Three Brothers

Case I (Figs. 1 and 2).—Male aged 34. Single.

Symptoms and signs.—He has had no illnesses and does a good day's work but is very nervous and has never had the slightest interest in the opposite sex. Libido, erections and emissions are absent, the testes are tiny but descended, prostate not felt.

Investigations.—Pituitary fossa normal.

Treatment.—He had 28,000 units of chorionic gonadotrophin in two months with an immediate

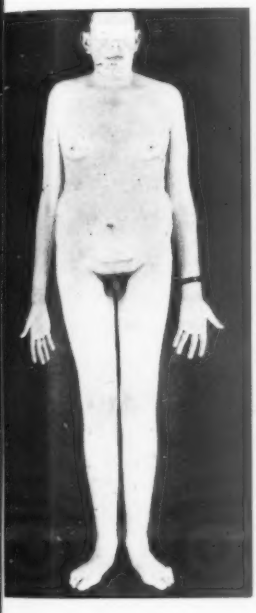

Fig. 3.

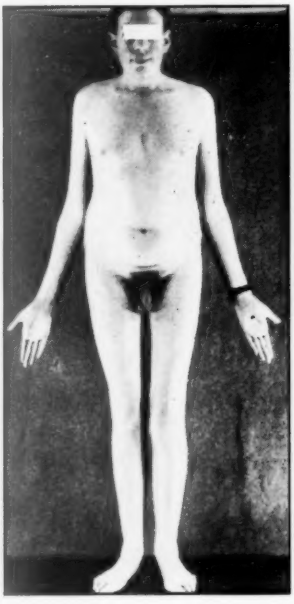

Fig. 4.

Fig. 10.—*Case* II, Section of testis.

Fig. 3.—*Case II*, M., 26 yr., single. 10.11.52. Ht. 72½ in. L.M. 41¼ in. U.M. 31¼ in. Diff. 10in. Span 78¾ in. Ep. age 16 yr. 17-K. 13 mg./24 hr. Testes very small. Voice unbroken. Gonadotrophin low.

Fig. 4.—*Case II*, 27.8.53. After treatment. Chorionic gonadotrophin 81,000 units. Methyl testosterone 900 mg. Thyroid grain i daily.

response consisting of heat and enlargement of the genitals and erections and such an exacerbation of libido as to render the world an entirely different place. Treatment was continued for six months with Pregnyl and small doses of methyltestosterone between the courses of Pregnyl. Fig. 2 shows enlargement of genitals and growth of pubic hair following six months' treatment, but the testes remain far below normal and there is no axillary hair. Mental improvement is striking. Before treatment semen could not be obtained, after treatment the seminal count was 3,500,000 per c.c., vol. 2 c.c. Condition regressed on stopping treatment. This was the severest case in the family and the biopsy of testis is the most removed from normal.

Biopsy of testis (Fig. 9) (done after treatment).—The testis is of immature type. Occasional spermatocytes are the most mature cells. There are no spermatids or spermia and a lumen is not present. Sertoli cells can be seen, Leydig interstitial cells are very deficient; the fibrous capsule is not thickened.

Case II (Figs. 3 and 4).—Male, aged 26. Single.

Patient has less than normal energy but hypogonadism is not quite so severe as in the preceding patient. Some libido, an occasional erection but no emission is present. Testes are very small but descended, the prostate is small.

Investigations.—Pituitary fossa large. Cholesterol 235 mg.%.

Treatment.—He had 28,000 units of chorionic gonadotrophin (Pregnyl) in two months, with a similar response to the previous patient. Treatment was continued for eight months with Pregnyl and small doses of methyltestosterone between the courses of Pregnyl. Before treatment semen could not be obtained, after treatment the seminal count was 2,600,000 per c.c., vol. 3 c.c. The testes enlarged almost to normal (Fig. 4). On stopping treatment for three months the patient's condition regressed.

Biopsy of testis (Fig. 10) (done after treatment).—In this section development is more mature than in Case I for it has proceeded in some tubules to spermia, in others only Sertoli cells and occasional spermatocytes are present. Sertoli cells are numerous, Leydig cells almost absent. Some of the fibrous capsules of the tubules are thickened.

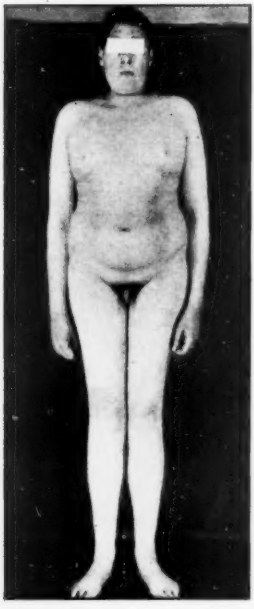

Fig. 5.

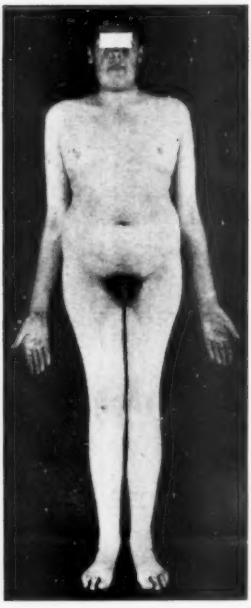

Fig. 6.

FIG. 5.—*Case III*, M., 29 yr., married. 5.1.52. Ht. 71¾ in. L.M. 40 in. U.M. 31¾ in. Diff. 8¼ in. Span 78 in. Ep. age 17 yr. 17-K. 6·5 mg./24 hr. Left testis small. Right testis in canal. Gonadotrophin low.

FIG. 6.—*Case III*, 11.9.52. After treatment. Chorionic gonadotrophin 74,000 units. Testosterone propionate 200 mg. Thyroid grain one-half, daily, for 6 months.

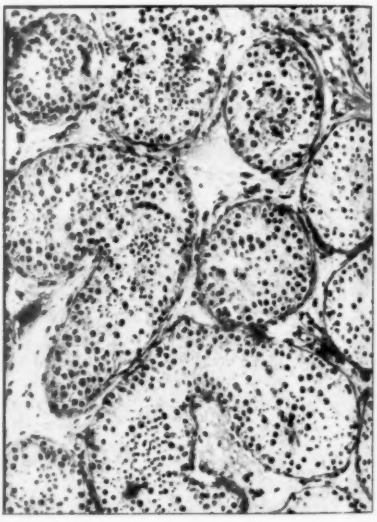

FIG. 11.—*Case III*, Section of testis.

Case III (Figs. 5 and 6).—Male, aged 29. Married, no children.

Symptoms and signs.—This patient resembles the previous two but is not quite so severe as he has married and has intercourse occasionally with small emissions. The left testis is small, the right testis is in the groin. The prostate is very small.

Investigation.—Pituitary fossa normal. Cholesterol 300 mg%.

Treatment.—He had 26,000 units of chorionic gonadotrophin and 200 mg. of methyltestosterone in two months, with immediate response. The genitals enlarged, the right testis descended. Libido was much increased, intercourse became normal. The colour of the skin improved and he became more energetic. No semen could be obtained before treatment, after treatment the count was 84,000 per c.c., vol. 1 c.c. The testes after six month's treatment are about two-thirds of the normal size. Condition regressed on stopping treatment.

Biopsy of testis (Fig. 11) (done after treatment).—Development is more mature than in either of the previous sections, the seminiferous tubules being cellular to the point of spermatid formation but spermia are relatively infrequent. Sertoli cells are present but Leydig cells are deficient. The tubular capsules are not notably thickened, the lumen is normal.

Two Sisters

Case IV (Fig. 7).—Female, aged 32. Married, no children.

Patient shows the same eunuchoid characteristics as her brothers. Axillary hair is normal, external genitalia are infantile and the uterus measures 1 in; periods have never been present; there is little mammary tissue with small nipples. She is happily married and has adopted a child; libido and intercourse are normal.

Investigations.—Pituitary fossa normal. Vaginal smear shows no œstrogenization. No curettings could be obtained from the uterus.

Treatment.—This has not been pressed as there is little to gain, for the patient is happy and satisfied. She has had a few courses of œstrogen and progesterone with some consequent cyclical bleeding.

Fig. 7.—*Case IV*, F., 32 yr., married. 19.1.53. Ht. 66 in. L.M. 38 in. U.M. 28 in. Diff. 10 in. Span 72 in. 17-K. 6 mg./24 hr. Ep. age about 21 yr. Cholesterol 225 mg.%. No periods. Uterus very small. Minimal breast tissue.

Fig. 8.—*Case V*, F., 28 yr., married. 5.1.53. Ht. 64½ in. L.M. 37½ in. U.M. 27 in. Diff. 10½ in. Span 72 in. 17-K. 4·6 mg./24 hr. Ep. age 16 yr. Cholesterol 310 mg.%. No periods. Uterus very small. Minimal breast tissue.

Case V (Fig. 8).—Female, aged 28. Married, no children.

Patient resembles her brothers and sisters. She is happily married and has normal energy, libido and intercourse. External genitalia are infantile, the uterus measures 1½ in.; mammary tissue is almost absent with small nipples. She has not adopted a child.

Investigations.—Pituitary fossa normal. Vaginal smear shows no œstrogenization. No currettings were obtained from the uterus.

Treatment.—Some substitution treatment produced cyclical bleeding.

Comment

The most interesting point in this family is the pituitary gonadotrophic defect while the other pituitary trophic factors are normal. This defect is presumably congenital. I have not found a similar

Case II (Figs. 3 and 4).—Male, aged 26. Single.

Patient has less than normal energy but hypogonadism is not quite so severe as in the preceding patient. Some libido, an occasional erection but no emission is present. Testes are very small but descended, the prostate is small.

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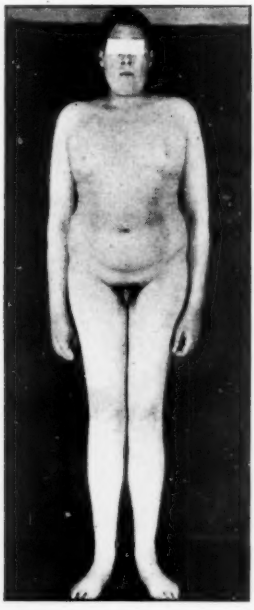

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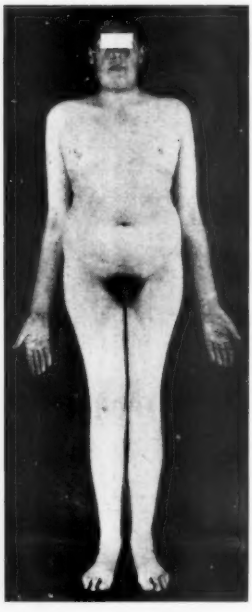

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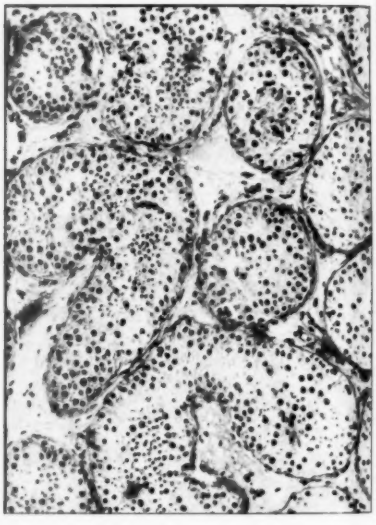

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Patient shows the same eunuchoid characteristics as her brothers. Axillary hair is normal, external genitalia are infantile and the uterus measures 1 in; periods have never been present; there is little mammary tissue with small nipples. She is happily married and has adopted a child; libido and intercourse are normal.

Investigations.—Pituitary fossa normal. Vaginal smear shows no œstrogenization. No curettings could be obtained from the uterus.

Treatment.—This has not been pressed as there is little to gain, for the patient is happy and satisfied. She has had a few courses of œstrogen and progesterone with some consequent cyclical bleeding.

Fig. 7.—*Case IV*, F., 32 yr., married. 19.1.53. Ht. 66 in. L.M. 38 in. U.M. 28 in. Diff. 10 in. Span 72 in. 17-K. 6 mg./24 hr. Ep. age about 21 yr. Cholesterol 225 mg.%. No periods. Uterus very small. Minimal breast tissue.

Fig. 8.—*Case V*, F., 28 yr., married. 5.1.53. Ht. 64½ in. L.M. 37½ in. U.M. 27 in. Diff. 10½ in. Span 72 in. 17-K. 4·6 mg./24 hr. Ep. age 16 yr. Cholesterol 310 mg.%. No periods. Uterus very small. Minimal breast tissue.

Case V (Fig. 8).—Female, aged 28. Married, no children.

Patient resembles her brothers and sisters. She is happily married and has normal energy, libido and intercourse. External genitalia are infantile, the uterus measures 1½ in.; mammary tissue is almost absent with small nipples. She has not adopted a child.

Investigations.—Pituitary fossa normal. Vaginal smear shows no œstrogenization. No currettings were obtained from the uterus.

Treatment.—Some substitution treatment produced cyclical bleeding.

Comment

The most interesting point in this family is the pituitary gonadotrophic defect while the other pituitary trophic factors are normal. This defect is presumably congenital. I have not found a similar

family in the literature. I had thought that a recessive gene was the explanation, but Professor L. S. Penrose, in a personal communication, states: "The main point which struck me is that you have 5 out of 6 children affected and if it were due to a recessive gene the expected incidence would only be 1 in 4. The chance against having 5 out of 6 affected on this hypothesis is considerable. Other possible genetical explanations would be some abnormal factor in the maternal constitution affecting all or nearly all her children but not the mother herself. If the mother's own parents were cousins a recessive maternal factor might be the cause. On the other hand an environmental condition, perhaps nutritional, might conceivably be implicated."

With reference to the mother it has not been possible to find out whether her parents were cousins. It is difficult to imagine a common nutritional factor in this family.

I am indebted to Dr. T. W. May of Swindon for co-operation; to Dr. G. I. M. Swyer for the gonadotrophin estimations, to Dr. J. Pinniger for the histological reports, to Mr. C. Latto for doing the biopsies and Mr. A. E. Clark for preparing the sections and photomicrographs.

The President (Dr. Raymond Greene): *Eunuchoidism and the Slipped Epiphysis*

In my recent Presidential Address to this Section I drew attention to the numerous repercussions of endocrinology on general medicine and surgery and on the various specialities. The following case illustrates this thesis. It is that of a eunuch of the tall thin type who suffered repeatedly from slipping of the epiphyses and whose condition was relieved by the combined action of testosterone and œstradiol.

The length of the "long bones" is determined by epiphyseal growth, growth in length ceasing

FIG. 1.—Before treatment.

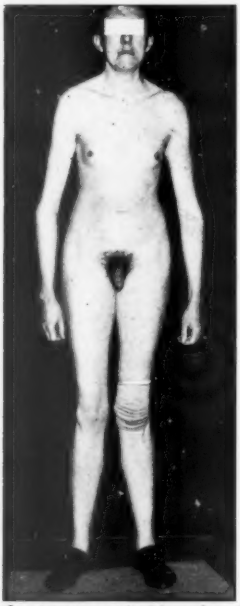

FIG. 2.—After treatment (subluxation, L. patella). Note slight gynæcomastia.

when osseous union occurs at the epiphyses. The actions of androgens and œstrogens on the epiphyses has been studied by numerous workers. The common observation that in general the male mature animal is larger than the female points to the fact that the action of œstrogens on the closure of the epiphyses is stronger than that of androgens. As long ago as 1877, Poncet showed that castrated male rabbits were larger than their normal litter-mates, the bones being longer, stronger and straighter, and the skulls also larger. His work was confirmed in 1905 by Richon and Jeandelize. In 1903 Launois and Roy described a case of a tall and slender eunuch of 27 whose epiphyses had persisted. Bouin and Ancel (1906) demonstrated a restraining action of testicular hormone on the growth of the bones of guinea-pigs. Nevertheless, the experiments of Steinach (1916), Steinach and Holzknecht (1916), Moore (1919 and 1922), and Pomerat and Coe (1941) show that castration does

not necessarily lead to increased length of bone. In interpreting this conflict of evidence, it is important to remember that the earlier workers who demonstrated the restraining effect of androgens were, in fact, using crude testicular extracts and not pure androgens. Where clinical observations are concerned, one must remember that the testicles produce œstrogenic as well as androgenic substances, and there is now a wealth of clinical evidence that pure androgens are capable of increasing growth. Webster and Hoskins in 1940 described the rapid upward growth of undersized hypogonad boys treated with testosterone propionate. No closure of the epiphyses occurred during treatment. Since then I have treated a large number of undersized boys with and without evidence of hypogonadism with methyl testosterone and methyl androstenediol and have confirmed their findings.

FIG. 3.—Knee joints before treatment.

FIG. 4.—Knee joints after treatment.

FIG. 5.—Knee joints before treatment.

FIG. 6.—Knee joints after treatment.

It is otherwise with œstrogens. It has been demonstrated very fully, notably by Tausk and de Fremery (1935) and by Gardner and Pfeiffer (1938) that in dogs and mice respectively, the administration of œstrogens leads to premature closing of the epiphyses. This corresponds with the observation that girls stop growing very soon after puberty, whereas boys may continue to grow in height into the early twenties.

The present case is that of a man of 29 under the care of Mr. E. T. Bailey at Highlands Hospital, who kindly asked me to see him. His story was that he had suffered very frequently in the past from effusions into the knee-joints (Figs. 3 and 5).

A sudden painful effusion, without any real trauma, occurred into the left knee in August 1949. He was admitted to Highlands, where slipped epiphysis was diagnosed, and treated by the usual orthopædic remedies but for one important difference. Mr. Bailey realized his lack of sexual development and implanted 400 mg. of testosterone. Despite this similar incidents followed in both knees in October 1949.

I saw him for the first time in January 1950. He was a very tall thin young man (Fig. 1) with soft skin, poor musculature, no beard, a high voice, scanty pubic and axillary hair, small penis and minute soft testicles. His weight was unfortunately not recorded. His height was 6 ft. 2 in. with a disproportionate length of leg (upper measurement 31 in., lower 43 in.). X-rays of the epiphyses gave a bone age of 18 to 19 years, his actual age at that time being 29. X-rays of the skull excluded hypopituitarism. Indeed the excessive hyperpneumatization suggested hyperpituitarism. His mental condition was of interest. His intelligence was high but he had no critical faculty, a good knowledge of electrical theory being combined with schemes for using it reminiscent of Dan Dare; and an interest in comparative religion leading him into much muddled philosophical thought. He was intensely interested in his disorder and given to forming rather wild ideas about its origins and possible methods of treatment. He was very fussy over his food. At a rehabilitation centre to which he went for a time, immense trouble was taken to get for him an extra ration of meat, but he would not eat it unless it was cooked exactly to his taste. He always preferred the company of men far younger than himself. With men of his own age he was often paranoid.

I recommended the implantation of 1 gramme of testosterone. Despite this he continued to grow and in March 1950 measured 6 ft. 2¼ in. and weighed 10 st. 6 lb. Male characteristics were making their appearance and he was shaving occasionally. I then implanted 500 mg. of testosterone and 300 mg. of œstradiol. Upward growth ceased immediately. His masculine characteristics continued to increase and his mental health improved. His previous excessive shyness gave way to a mild aggressiveness. By May 1950 his weight was 11 st. 9 lb. No further slipping of the epiphyses occurred (Figs. 4 and 6). Further implants were given, of 1,000 mg. of testosterone and 300 mg. of œstradiol, in November 1950.

He has had no further implantations because his epiphyses have closed. He had an accident in April 1952 in which he suffered subluxation of the patella without injuring his epiphysis (Fig. 2). From the sexual angle he has retrogressed, but he finds it easier to maintain a good mental adjustment without substitution therapy.

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Section of Orthopædics

President—H. L-C. Wood, M.S., F.R.C.S.

[*February* 2, 1954]

Recurrent Paraplegia Following Antero-lateral Decompression.—J. H. Shelswell, F.R.C.S. (for H. J. Seddon, C.M.G., F.R.C.S.).

L. W., a Jewish woman, aged 46.

When first seen she was complaining of pain in the mid-dorsal region which had been present for fourteen months. X-ray showed tuberculous disease of the 6th and 7th thoracic vertebræ with a small abscess. After six months in a plaster bed and a full course of streptomycin and para-amino-salicylic acid she was discharged as quiescent, wearing a Fisher type support.

Twenty-eight months after the onset of the disease she developed further pain; examination showed further activity of the disease and mild paraplegia. This failed to respond to conservative treatment and costotransversectomy was therefore performed, releasing 10 c.c. of caseous pus. The paraplegia persisted, however, and antero-lateral decompression of the spinal cord was performed ten weeks later revealing that the paraplegia had been caused by a prominent piece of bone, part of the lower vertebra involved in the disease. There were several small sequestra present and these were removed. Rapid recovery of the paraplegia followed.

Fig. 1.—Showing sequestrum of vertebral body.

Three months later a spinal fusion of the affected segment of the spine was performed and after a further three months' immobilization the patient was discharged.

She was well for eleven months after this (November 1953), when she noticed a return of the weakness in the right leg and examination revealed a recurrence of the paraplegia. X-ray showed involvement of another vertebra above those already affected with a large sequestrum lying against the spinal cord (Fig. 1). Lumbar puncture showed that the cause of the paraplegia was mechanical rather than inflammatory. The paraplegia did not improve with eight weeks' immobilization in a plaster bed and therefore a second antero-lateral decompression was undertaken (January 12, 1954). This revealed a large globular abscess pushing the spinal cord back against the laminæ and containing thick caseous pus and five large sequestra. There was no pulsation present in the spinal cord. Recovery of the paraplegia was rapid following this operation and apart from extensor plantar responses there is no evidence of paraplegia now.

This case was presented as the only known case of recurrent paraplegia requiring antero-lateral decompression on two occasions.

Pseudarthrosis of Tibia Treated with Four-pin Compression Clamp.—A. C. Bingold, F.R.C.S.

A 3-year-old boy was admitted on 18.9.50 with osteomyelitis of his left tibia. Treatment included antibiotics, incision of a subperiosteal abscess and guttering of the lower end of the tibia. In spite of a long leg plaster applied after the guttering he sustained a pathological fracture near the ankle. After six months' immobilization in a plaster spica (Fig. 1), followed by double maternal onlay grafts and packing of osteo-periosteal shavings round the fracture and nine months' immobilization there was still non-union (Fig. 2).

On 23.10.52 the fibula was divided obliquely and the tibial fragments, which consisted chiefly of soft bone, were freshened and compressed with a four-pin clamp. A long leg plaster was applied and the limb was suspended from an overhead beam. Two months after the operation the fracture was

FIG. 1.

FIG. 2.

FIG. 1.—Non-union after plaster immobilization for six months.

FIG. 2.—Non-union after double maternal onlay grafts.

FIG. 3.—Union two months after application of clamp which is still in situ.

FIG. 4.—Narrow and irregular tibial epiphysis, low fibular malleolus and varus of heel fifteen months after the last operation.

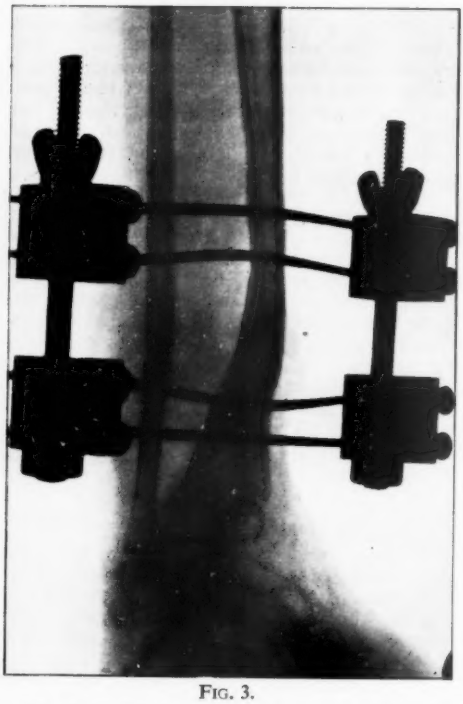


FIG. 3.

FIG. 4.

Mr. A. C. BINGOLD: *Pseudarthrosis of Tibia Treated with Four-pin Compression Clamp*

united (Fig. 3) and the pins were removed, but immobilization in plaster without weight bearing was continued for another three months. Within a few days of removal of the plaster the child walked normally.

Fifteen months after his last operation he could pursue normal activities. The physical signs then were slight wasting of the left calf, prominence of the left fibular malleolus, slight varus of the left heel (Fig. 4) and ⅜ in. of shortening. His left foot was 2 sizes smaller than his right. The shortening and the varus of the ankle may demand further surgery.

In the subsequent discussion several members cited cases in which union had been obtained by compression. **Mr. Bingold** stated that he believed union to be accelerated by increasing the area of bony contact at the fracture site, and showed by an ingenious mechanical model that the pressure exerted in the cortex at each transfixion hole was in the order of 1,000 lb. per square inch.

Infantile Cortical Hyperostosis.—R. H. MAUDSLEY, F.R.C.S. (for C. H. GRAY, F.R.C.S.).

K. M., female infant aged 3 months. First seen 7.9.53, when the mother stated that the child did not use the left leg, which was tender and swollen. The child had been irritable and not feeding well for two or three weeks.

Normal birth. First child. Breast fed. No relevant family history.

On examination the infant looked healthy and well nourished. The temperature was 99·4° F. Pulse 128/minute and respiration 28/minute. There was no lymph gland enlargement.

Left lower limb—there was tenderness and a fusiform swelling of the left femur. There was no fluctuation or reddening of the skin, which was freely mobile. The knee was held in 30 degrees flexion, and movements were resisted.

X-rays: The shaft of the left femur was enveloped by periosteal new bone formation with some extension posteriorly into the soft tissues (Fig. 1).

FIG. 1.—*Left femur* (18.9.53). Subperiosteal new bone formation of the whole shaft, with irregular extension posteriorly.

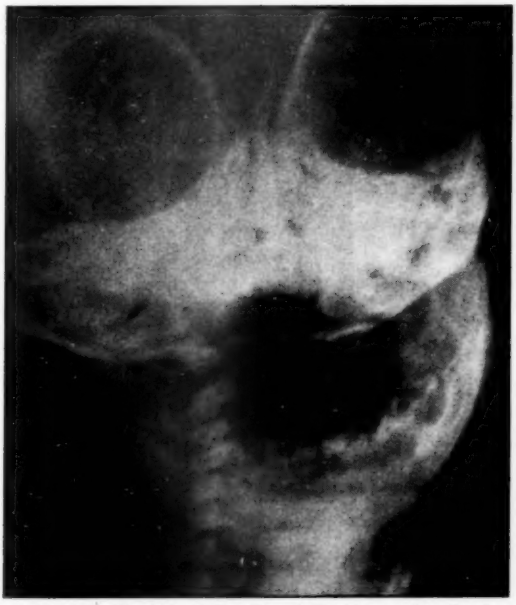


FIG. 2.—*Mandibles* (27.9.53). "Shadow-outline" of mandible, more obvious on the left side.

Investigations:

Blood: E.S.R. 75 mm. in first hour (Westergren). R.B.C. 3,170,000/c.mm. Hb 55%. W.B.C. 17,300/c.mm. (with relative lymphocytosis). Group A Rh positive.

Throat: No abnormality.

Urine: No abnormality.

21.9.53: No change clinically; mild pyrexia. A course of penicillin was commenced but produced no change.

Biopsy of femur revealed no abnormality in the tissues until the periosteum was divided. The cortex was very friable and splintered when being cut. The medulla was normal. No hæmorrhage, pus or tumour tissue was encountered.

Biopsy report (Dr. A. G. Stansfield).—(1) Sections of the bone show a well-developed layer of periosteal reactive new bone on the surface of the cortex. The marrow appears normal. There is no evidence of osteomyelitis or new growth and the appearances are rather suggestive of a healing fracture.

(2) Section of the soft-tissue fragment shows œdematous skeletal muscle.

22.9.53: E.S.R. 52 mm. in first hour (Westergren). W.B.C. 9,600/c.mm.; relative lymphocytosis.

27.9.53: Tender swelling developed in the left mandible. Jaw movements were restricted. There was a mild rise in temperature (100° F.).

X-rays showed cortical thickening of the mandible, the left half more than the right with a "shadow outline" (Fig. 2). The whole skeleton was X-rayed but no further abnormality was seen. The subsequent clinical course was uneventful. No further swellings developed and those in the left femur and mandible gradually dispersed.

2.2.54: The child was healthy and kicked her left leg actively. There was still some thickening present but this was not tender. Hip and knee movements were full. There were no swellings palpable.

Discussion.—This case presents the essential features of infantile cortical hyperostosis as described by Caffey in 1946. The differential diagnosis is made after consideration of other causes of periosteal new bone formation, namely trauma, osteomyelitis, syphilis, scurvy, hypervitaminosis A, and neoplasm. The ætiology is obscure, but the multiplicity of lesions, pyrexia, leucocytosis and raised E.S.R. point to an infectious source, possibly a virus.

There is no evidence of any treatment influencing the course of the disease. In this case a second lesion occurred while penicillin was being administered.

This condition may be commoner than would appear from 50 cases recorded mostly in the U.S.A.

REFERENCE: Caffey, J. (1946), *J. Pediat.*, **29**, 541.

Infantile Cortical Hyperostosis.—M. B. Devas, M.B., F.R.C.S. (for Philip Wiles, M.S., F.R.C.S.).

J. M., female, aged 2½ years.

In May 1953 this child, then aged 21 months, was admitted to hospital complaining of pain in the right leg which was swollen and tender.

X-rays showed a mass of subperiosteal new bone on the shaft of the right tibia (Fig. 1A). The left tibia was normal.

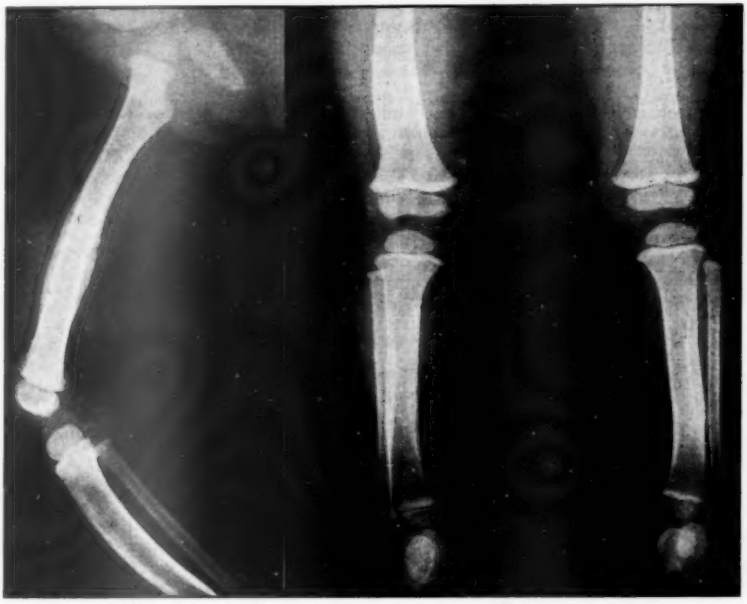
A B

Fig. 1.—A, The right tibia in May 1953. The accentuation of bowing is seen clearly.
B, Left tibia, August 1953, when first affected.

By June the new bone was absorbing and the child was discharged, only to be readmitted in July 1953, with a similar condition in the left tibia (Fig. 1B). For a few days she ran a fever up to 100° F.; intensive investigations including the Mantoux and Wassermann reactions and the ascorbic acid saturation test were negative, but there was a relative lymphocytosis.

Apart from a mild intercurrent urinary infection convalescence was uneventful and the new bone began to absorb. She was discharged in October.

She then remained well until January 1954, when her doctor noted her right thigh was swollen and that she was stumbling a lot, though not complaining of pain. She was readmitted and the right femur showed the typical radiological changes (Fig. 2A). The new bone on the tibiæ was absorbing well (Fig. 2B).



A B

FIG. 2.—A, Right femur in January 1954, showing the typical new bone. B, The tibiæ in January 1954, showing good resolution.

Past history.—One of three children abandoned by the parents. She has lived in a County Council residential nursery on a good diet and has had no feeding difficulties. She has had no serious illnesses.

Family history.—Her elder brother at the age of 1 year was under the care of another hospital and was diagnosed as "a case of Caffey's Cortical Hyperostosis, though not quite typical".

Comment.—The interesting features of this case are the age of onset, the family history and the absence of facial involvement.

Walley (1953) described a case and summarized 43 more from the literature. To these can be added 6 more (Bauman and Lubell, 1949; Thompson, 1948; Berkheiser, 1949; Chen and Yu, 1948; Larkin and Rousseau, 1950). Of these 50 cases all except 4 were under 6 months old at the time of onset. The 4 exceptions were all between 20 and 30 months old when first affected; in none of these 4 was the mandible involved although it was in at least 31 of the other 46. Caffey (1946) felt that the older group might not perhaps be valid examples of the syndrome. However, our patient has a family history suggesting that the condition is the same and Van Zeben (1948) has also recorded the condition in a brother, sister and second cousin.

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Old Tuberculous Left Hip and Flail Right Knee.—R. H. METCALFE, M.D., M.Chir., F.R.C.S.

J. S., male, aged 45.

1917: Patient buried in bombing incident sustaining an injury to the left hip which was probably a separation of the upper femoral epiphysis.

1921: Three years in Princess Mary's Hospital, Margate, with "T.B. left hip and right knee". Patient has been at work since 1925 but has had considerable disability resulting from gross deformity of the right hip which was held in 30 degrees flexion, 20 degrees adduction and 30 degrees external rotation. He can only walk by holding the right knee in intense degree of genu valgum and this again resulted in gross weakness of the internal lateral ligament and gross lateral laxity of the knee-joint. To allow the right leg to pass the left in walking he had to hold the left knee in genu varum. This has caused increasing pain in both knees and he has had to stop his work. The case was shown so that opinions might be obtained as to the best treatment in this difficult case. The various suggestions are set out below:

(1)	Subtrochanteric osteotomy to correct adduction and external rotation	12
(2)	McMurray osteotomy to correct adduction and external rotation	4
(3)	Judet arthroplasty	2
(4)	Girdlestone operation	1
(5)	Arthrodesis	Nil
(6)	Cup arthroplasty	Nil

FIG. 1.—Before operation.

FIG. 2.—After operation.

POSTSCRIPT.—The first method was decided upon and the operation was carried out on 22.2.54. Fig. 2 shows the position after operation. The fixed flexion was not corrected as the present degree of flexion was satisfactory. Patient discharged from hospital on 1.6.54 walking with two sticks with deformity fully corrected.

"Genuine" Congenital Dislocation of the Hip.—R. H. V. HAFNER, F.R.C.S.

History.—Male, born 10.9.53; Birth weight 6 lb. 8 oz. Normal pregnancy; normal delivery. Mother noticed that the child's feet were abnormal, and brought him to hospital when 5 weeks old. He was found to be suffering from congenital dislocation of the left hip, and had, in addition, the following congenital abnormalities: (1) Bilateral varus deformities of feet—right worse than left (not severe); (2) bilateral inguinal herniæ; (3) umbilical hernia.

FIG. 1.

X-ray examination (16.10.53) showed left congenital dislocation of the hip (Fig. 1).

Family history. — Father, Indian. Mother, English. One sister, aged 4½ years. No congenital defect of mother, father or sister.

An attempted reduction of left hip by closed manipulation under general anæsthesia (ether) was performed 20.10.53 when it was found completely impossible to move the head at all from its false position.

The infant has been seen at frequent intervals since, and Denis Browne splints applied to the feet, which are now almost normal. The inguinal and umbilical herniæ are no longer apparent. The left hip remains unchanged.

Le Damany (1904–1907) described a rare group of "Teratological" dislocations of the hip, present at birth and usually combined with other severe malformations frequently incompatible with life. Lorenz (1920) distinguished "Genuine" congenital dislocation from the "So-called" congenital type, which he described as being bilateral, combined with other congenital malformations, and irreducible.

In the discussion **Mr. K. I. Nissen** was in favour of the diagnosis of arthrogryphosis, and other members suggested that treatment by traction in an abduction frame offered some hope of improving the present position.

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Pes Plano Valgus in School Children.—W. H. GERVIS, F.R.C.S.

In a normal footprint (Fig. 1) the outer border of the foot is weight-bearing throughout its length, suggesting that the arch-like appearance on the medial side of the foot is not a true arch, because it is supported in the middle of its span. Radiographic examination of a normal foot, standing, affirms this suggestion (Fig. 2). The fifth metatarsal is resting upon the ground throughout its length, and the cuboid is resting upon its base. Now the articular facet on the cuboid for the cuneiform is not on the medial surface, it is at an angle of 50 degrees to vertical so is more nearly on the dorsal surface. Thus the cuneiform rests upon the cuboid. The talus is resting posteriorly upon the calcaneum, which, in turn, is on the ground and anteriorly it rests firmly on the cuboid. Considered in this way the arrangements of the bones of the foot could be compared to a rough wall. Such a comparison has advantages

FIG. 2.—Tracing of radiograph of normal foot standing. Lateral view.

FIG. 1.—Pes plano valgus standing on glass stool, with deformity corrected by correcting his balance as taught. Note the footprint in mirror, which is now normal, with outer border of foot weight-bearing.

FIG. 3.—Pes plano valgus, posterior view. The whole foot is leaning over to medial side.

FIG. 4.—Same case as Fig. 3. Deformity corrected by correcting balance.

for the behaviour of the foot resembles that of a wall. A wall will remain upright because one stone is balanced upon another. If the balance is upset it will lean over and eventually fall to one side. In a pes plano valgus the foot is leaning over to the medial side (Fig. 3). This deformity can be corrected by correcting the balance (Fig. 4), except in cases of long duration. The calcaneum is now vertical and not

leaning over, with the talus balanced upon it. In normal standing the femur is balanced upon the tibia, so balance appears to be a more reasonable explanation of why the foot remains upright, than the complicated theories in support of an arch.

In order to examine these cases, a stool with glass top and mirror beneath was used, which gave a view of foot and footprint at the same time. In all the earlier cases of pes plano valgus it was found that the footprint was that of an arch, resembling a pes cavus in that the outer border was not weight-bearing (Fig. 5). Therefore in the first stage of this deformity the whole foot is tilted over to the medial side and the outer border has left the ground. The weight is now taken by the heel and head of first metatarsal, and the medial longitudinal arch really becomes an arch, for it is no longer supported in its span. By correcting his balance the patient can correct the deformity, and a normal footprint results (Fig. 1). Had this case remained untreated the first metatarsal segment would have given way under the excessive weight thrown upon it, the first metatarsal becoming dorsiflexed until the outer border of foot is weight-bearing again. This altered position of the first metatarsal would give the classical footprint of a pes plano valgus.

Thus the various stages of flat-foot, from a slight valgus deformity of ankles to a severe pes plano valgus, depend upon the degree to which the foot is leaning over, and to what extent the first metatarsal has been dorsiflexed as a result. The majority of these school children can correct the deformity by correcting their balance. In some the deformity is a simple one, and the foot is just leaning over. In a greater number there is some rotation of the talus. Such cases stand with the knees pointing toward the mid-line (Fig. 6, and to some extent in Fig. 5). Thus the leg, ankle and talus are rotated medially in relation to the foot. This rotation of the talus carries the cuneiforms and the body weight to the medial side of the foot, upsetting its balance. In many cases this rotation may arise from or be associated with out-toeing. Most cases can correct this deformity by correcting the balance. To do so they must brace back the knees and rotate them in an outward direction until they face in the direction of the feet (Figs. 1 and 4).

FIG. 5.—Pes plano valgus, same case as Fig. 1, standing with deformity uncorrected. Feet are leaning over to medial side, slight internal rotation of knees. Typical early pes plano valgus footprint in mirror, outer border of foot not weight-bearing, weight taken by heel and head of first metatarsal.

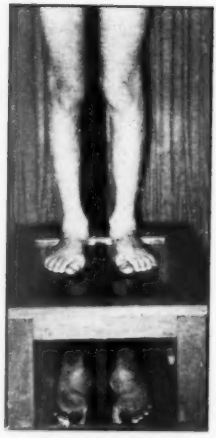

FIG. 6.—Pes plano valgus associated with severe internal rotation of knees. Case of longer duration and footprint therefore tending to classical plano valgus type.

In congenital malrotation of tibia the same rotation of talus will occur if the child stands with feet parallel, but the knees will not be pointing in.

To my mind the various current methods of treatment do not correct this deformity.

Arch supports do not correct the rotation of the talus. They are designed to withstand the vertical

thrust of an arch collapsing, but not the medial thrust of the foot leaning over. They are harmful in that they prevent active use of the foot in walking.

Wedging the inner side of the heel.—If the foot will not balance upright on a flat surface, there appears to be no reason why it should do so on an inclined plane. This method is therefore uncertain. All additions of leather to a shoe make it heavier and stiffer, so more difficult to walk in properly.

Exercises.—Few of the routine flat-foot exercises correct the deformity. Some are harmful. "Making the arch of the foot", for example, does not bring down the head of the first metatarsal, on the contrary the first toe is flexed and pushing it up. Thus we are teaching the child to try to correct the balance by means of the first toe. If he is an apt pupil this will lead to a hallux flexus and later a hallux rigidus.

The treatment that has been used and found successful consists of teaching these children how to stand in a position of correct balance, and also how to walk. The latter is necessary because in the ordinary gait of a child wearing stiff shoes there is no active use of the foot. In such a gait the natural mechanism which pulls the calcaneum into the vertical position when rising up on the toes is never used. We therefore teach these children to rise up on the toes of the carrying leg as the after-coming leg comes forward. By so doing when they come to stand the foot is not leaning over, but ready for them to balance correctly.

A few cases cannot correct the deformity because it is old-standing. In these the deformity is first corrected, and held thus in plaster of Paris casts in which the children walk for six weeks, or until they have learnt correct balance.

All the children attend classes where they are taught by a physiotherapist to stand in a position of balance with the deformity corrected. Some will need manual assistance at first to help in external rotation of knees, and to see that the head of the first metatarsal is on the ground, heel vertical, toes not contracted. They are taught to stand thus always.

They are also taught to walk. Some children find it difficult to rise up on the toes of the carrying leg. A useful exercise to develop this gait is as follows. The child stands holding the side of a chair for balance, left foot in front of right, feet not pointing out. He then brings right foot forward past left as in a step, rising up on toes of left as he does so. Then right foot back and repeat. When he can do it on left foot, then practise on right. In teaching this gait it must not be exaggerated or too springy. We are trying to teach a gait that is to be used always. After three months the majority of children can stand and walk correctly. It is important that they should be seen again in a further three months, for a certain number relapse, and require a refresher course of training.

I have no doubt that these common deformities could be prevented to a large extent. I would therefore suggest that the first essential of the physical training, which all these children have at school in one form or another, is to teach them how to stand and how to walk. The present instructors will be able to teach them this with proper guidance from orthopædic surgeons. It is also necessary to continue the campaign to rid the public of the idea that the foot needs support before the shoemakers will produce a really proper shoe.

Unusual Rheumatoid Arthritis (Arthritis Mutilans).—H. GORDON MATHER, M.A., M.B., M.R.C.P.

Miss M. K., a 36-year-old clerk, in 1941 developed pain and swelling in the finger-joints, principally the proximal interphalangeal joints. During the following year the knees, wrists, elbows and shoulders were similarly affected. A course of gold and prolonged physiotherapy were given without benefit. In 1943 the pain gradually disappeared from the fingers, and many of the joints became excessively mobile. In consequence she was able to play the piano and write; these faculties are still preserved. The other affected joints, however, remained painful and became progressively more fixed.

At intervals since the age of 11 she had four attacks of parotitis on the left side, which on each occasion subsided spontaneously within a week. She also noticed recurrent redness in the left eye but there had been no pain or blurring of vision.

FIG. 1.—Hands showing redundancy of skin in the little fingers and hyperextension.

Physical examination.—Weight 48 kg. Afebrile.

There was bilateral keratoconjunctivitis sicca from tear deficiency, typical of Sjögren's syndrome. The lacrimal and salivary glands were not enlarged, but there was slight lymph-node enlargement on the right side of the neck and the spleen was just palpable. Examination of the chest and cardiovascular system revealed no abnormality. The hands (Fig. 1) were deformed by swellings of many of the finger-joints and wasting of the small muscles. Many joints, especially the proximal interphalangeal joints of the thumbs, little fingers and right index finger, were capable of hyperextension, abduction

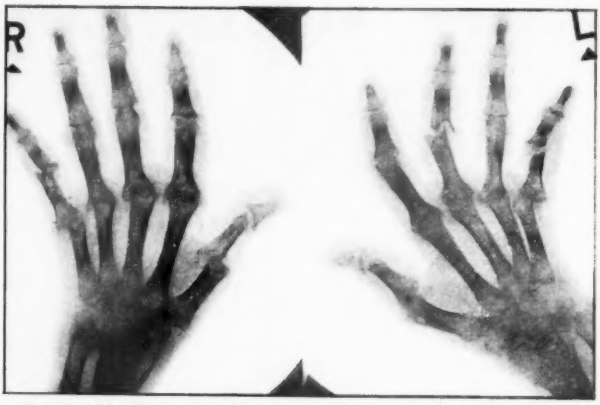

FIG. 2.—Hands: remarkable bony destruction around the proximal interphalangeal joints of several digits.

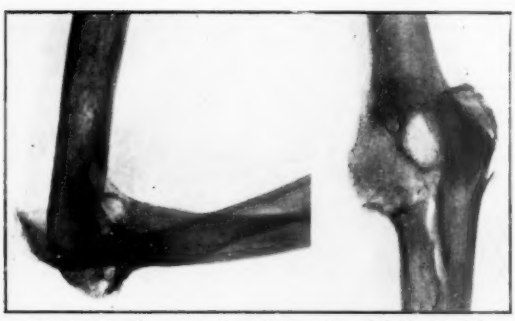

FIG. 3.—R. elbow: marked destruction of the bone ends resembling a Charcot joint.

FIG. 4.—L. knee: secondary osteosclerosis with ankylosed patella.

and adduction without pain. In these digits there was shortening and consequent redundant folds of skin. The wrists were in flexion deformity with only 10 degrees range of movement. Full flexion was possible in the elbows but extension was limited to about 100 degrees; there was marked periarticular thickening and several subcutaneous nodules. The humero-scapular and knee-joints were almost ankylosed, but movement in the hips was almost normal and pain-free. Detailed examination of the central nervous system showed no abnormality.

Radiographs.—The hands (Fig. 2) showed marked osteoporosis around the inflamed joints and loss of joint space, with actual destruction of the bone ends in several proximal interphalangeal joints. There was a more pronounced destruction of the bones around the elbow-joints (Fig. 3). In the knees there were secondary sclerotic changes with bony ankylosis of the patella (Fig. 4) whereas in the shoulders osteoporosis was the main feature. The radiograph of the pelvis showed large "cysts" in both femoral necks (Fig. 5). There was no evidence of generalized decalcification and in particular the skull, spine and teeth were within normal limits.

FIG. 5.—Hip-joints: large cysts in R. femoral neck, smaller in L.

Investigations.—The E.S.R. was 83 mm. in the first hour (Westergren) and the hæmoglobin 10·7 grammes/100 ml. (72%) from an iron deficiency anæmia. Examination of the urine was normal, as were the blood urea and uric acid; the Wassermann reaction was negative. There was no evidence of primary or secondary hyperparathyroidism after investigation by calcium balance.

Biopsy of a subcutaneous nodule showed the typical changes associated with rheumatoid arthritis. Because of the obscure nature of the cysts in the femoral necks, a biopsy was performed by Mr. H. L-C. Wood. Necrotic material and fluid resembling pus was obtained which was sterile on culture. Histological study showed areas of necrosis of non-specific appearance, the surrounding bone was normal and showed no inflammatory reaction.

Comment.—Many of the features of this patient's illness were typical of rheumatoid arthritis—the long history of polyarthritis affecting the usual joints, the enlarged spleen, raised E.S.R., anæmia, and typical skin nodules. The excessive and painless mobility of some of the finger-joints was extremely unusual, as was the bony destruction there and in the elbows. These findings were suggestive of neuropathic joints, but a careful neurological examination showed no abnormality, nor was there any history of peripheral neuritis. The appearances agree, however, with the diagnosis of arthritis mutilans. A severe example of this end-result of chronic rheumatoid arthritis was first described by Marie and Léri in 1913, who aptly described the hand as "la main en lorgnette" because of the telescoping of the fingers. They found the bone destruction at necropsy was due to gross fatty degeneration. No explanation of the pathogenesis has been forthcoming, and one can only speculate that perhaps the severe inflammation destroys the pain and trophic fibres in the joint and periosteum.

The other remarkable feature in this patient was the presence of large "cysts" in both femoral necks despite the absence of clinical signs in the hip-joints. There had been occasional pains there but examination showed a good range of movement which was painless. The bone biopsy revealed non-specific necrosis with no evidence of neoplasia, a lipoidosis or increased osteoclasis. The conclusion is that these necrotic areas are an integral part of the rheumatoid arthritis, albeit in an unusual site.

I wish to thank Dr. Clifford Hoyle for permission to describe this patient, Dr. J. Blewett for the radiographs and Dr. D. R. Rushton for the histology.

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Congenital Absence of the Lower End of the Tibia.—JAMES BRIGGS, F.R.C.S. (for R. C. F. CATTERALL, M.Ch., F.R.C.S).

The girl was born on March 9, 1952, with a very severe degree of talipes equinovarus. The foot was rotated medially through 180 degrees and the big toe was producing an indentation in the front of the leg. X-ray (Fig. 1) examination showed absence of the lower end of the tibia and a widening of the space between the tibia and fibula. X-ray of the hips was normal.

The child was treated at first by manipulation and splinting with Denis Browne splints, and subsequently by repeated plaster casts. On April 15, 1953, operation was performed by Mr. Catterall. The tendo achillis was lengthened and posterior capsulotomy of the ankle and subtaloid joint was

carried out. A fair correction was obtained and has been maintained since, at first by plaster casts and later by polythene splints.

FIG. 1.

At present the child is aged 1 year 10 months. The foot is still slightly inverted and it has not been possible to obtain further correction during the past six months. The affected limb is 1½ in. short. There is a full range of knee movements and a fair range of active movement in the joints of the foot. Correction is being maintained by a polythene splint but the child is showing little inclination to walk.

In the subsequent discussion it was generally agreed that no useful purpose would be served by any local surgery. The question of amputation was discussed fully but the majority opinion was in favour of maintaining correction by appliances until the child was old enough to decide the question for herself.

Section of Obstetrics and Gynæcology

President—VICTOR LACK, F.R.C.P., F.R.C.S.Ed., F.R.C.O.G.

[*January* 22, 1954]

Dysgerminoma of the Ovary.—ALICE BLOOMFIELD, F.R.C.S.

This patient, Miss C., aged 21, single, was referred to me by her private doctor on 12.11.43, with the complaint of acute abdominal pain occurring some two weeks before and accompanied by vaginal hæmorrhage.

The patient looked ill and pale. On abdominal examination there was some distension, and a tender somewhat elastic tumour was present arising from the pelvis on the right side. On vaginal examination, the uterus could be felt pushed forwards and to the left by a tumour arising from the right side of the pelvis.

Laparotomy was performed on 16.11.43 when a large soft tumour was found replacing the right ovary and very adherent to the pouch of Douglas.

This was removed and the rather free bleeding controlled by hot gauze packs. The uterus and left ovary were normal and were left in situ.

Microscopic examination showed this to be a dysgerminoma of the ovary, the tumour consisting of characteristic large rounded clear cells arranged in alveoli or nests, separated by septa of fibrous material showing more or less hyalinization, and, quite constantly, the extensive lymphocytic infiltration common in these tumours.

As the tumour was considered to be very anaplastic and malignant, it was decided after considerable hesitation to give the patient deep X-rays which were carried out at the Marie Curie Hospital. These were given by four portals of entry between 13.12.43, and 7.1.44, the total skin dose being 9,200 r. The patient has remained well ever since.

Endometriosis Including Endometriosis of the Diaphragm and Meigs' Syndrome.—ALAN BREWS, F.R.C.O.G.

The patient was a married woman, aged 39, who presented with gross ascites and a total right pleural effusion and who was ultimately shown to have diffuse abdominal endometriosis with multiple foci in the peritoneum and widespread involvement of the right side of the diaphragm with a small communication through it between the peritoneal and right pleural cavities.

The patient has enjoyed excellent health for three and a half years following the irradiation of her ovaries to create an artificial menopause.

Cystic Endometrioma of the Uterus.—DOREEN DALEY, M.D., F.R.C.S.Ed., M.R.C.O.G.

A single woman, aged 34, working as a housemaid, first attended hospital on 20.4.53 complaining of blood-stained vaginal discharge for the past ten weeks.

The *menstrual history* was that her periods started at the age of 13 and she had continued to lose regularly for three to four days each month until 6.2.53, when menstruation began normally but was followed by slight bleeding which had continued. The loss was never heavy and no clots had been passed. There was no history of dysmenorrhœa but, since the abnormal bleeding started, she had noticed slight aching across the lower abdomen. The *past history* was negative and on *symptomatic enquiry* she stated that she had not noticed any change in micturition, bowel habit, weight or abdominal size. She felt very well except for slight dyspnœa on exertion.

Examination showed a pale but otherwise healthy-looking woman. Palpation of the *abdomen* showed a hard, irregular rounded mass rising from the pelvis near the umbilicus. It was slightly tender and mobility was limited. There was no evidence of ascites or liver enlargement. Slight red loss was noted on *vaginal examination* and the mass felt abdominally was found to be continuous with an irregular pelvic mass from which the uterus could not be differentiated. The cervix felt normal.

The most likely *diagnosis* appeared to be uterine fibroids but in view of the prolonged bleeding and the chance that the tumour might be a malignant ovarian neoplasm, early admission to hospital was arranged. When she came in on 5.5.53, she said that the bleeding had ceased three days previously. General examination was essentially negative except for anæmia (hæmoglobin 53%). In

view of her age, conservative surgery was planned if the tumour was innocent and if technically feasible but she was asked to give consent for hysterectomy if it was considered desirable. She willingly agreed to this, adding that she would prefer it to any risk of recurrence of trouble later on. Before laparotomy she was given a blood transfusion and also examined under anæsthesia to rule out uterine malignancy. The findings were a normal cervix and a normal uterine cavity with metropathic curettings. The main tumour appeared to arise from the fundus uteri. When the abdomen was opened on 11.5.53, no ascites was seen and a large polycystic tumour presented in the wound. This was taken to be an ovarian tumour until closer inspection showed that it arose from a broad pedicle near the fundus of an apparently normal uterus. The appendages looked normal except for some small follicular cysts in the ovaries. In view of the doubtful nature of the tumour, the fact that she did not mind losing her uterus and, in any case, suffered from metropathia hæmorrhagica that might be recurrent, pelvic clearance was performed. During convalescence and subsequent follow-up, she did well.

Pathology.—I am indebted to Dr. Magnus Haines for the following pathological reports on the specimen which was sent to him uncut for the Rare Tumour Registry:

Macroscopical.—The uterus measures 6 × 4 × 4 cm. and attached to the left posterior wall by a short pedicle, 3·5 cm. thick, there is a polycystic tumour 16 cm. in diameter. Two small subserous cysts are present on the anterior wall and a few more on the posterior surface. The interstitial portion of the right tube shows altered blood and the ovary simple cysts (Fig. 1).

Fig. 1.

Microscopical.—The peritoneal surface of the *uterus* shows a small endometrial cyst. The endometrium is atrophic and cystic. The *tumour* is composed of numerous cysts of varying size, set in fibromuscular tissue. The epithelium is endometrial in type and occasionally carries a mantle of stroma cells.

The right tube shows chronic inflammation and is distended by old and recent blood clot. The left tube shows fibrosis only.

The ovaries show follicular cysts but no endometriosis.

Commentary.—Localized uterine tumours containing endometrial elements are much more rare than diffuse adenomyosis but cases are described by Haines (1947), Mahfouz (1949) and others. Macroscopic endometrial cysts in the uterus have been described by Gold and Kearns (1945).

Unusual features of this specimen appear to be the great size of the cysts, but superficial attachment, the relative absence of bleeding into them and, microscopically, the paucity of muscular tissue.

According to Novak (1952), "a genuine endometriosis of the uterus, with little or no muscle admixture, is seen in cases in which a pelvic endometriosis attacks the uterus from without, involving most commonly its posterior serous surface and the immediately underlying muscularis, though such a lesion is only a part of a more general pelvic endometriosis". This description seems to fit our specimen but it is interesting that the only evidence of endometriosis apart from the main tumour lies

in the multiple tiny cystic areas seen on the peritoneal surface of the uterus. The absence of endometriosis in the ovaries and its entirely surface but multicentric distribution in the uterus would seem to favour the serosal metaplasia theory of origin, at least in this particular case.

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Adenocarcinoma of the Cervix from a Patient (Gravida V) of 23 Years. Wertheim's Hysterectomy on the Seventeenth Day of the Puerperium.—J. R. E. JAMES, F.R.C.S.Ed., M.R.C.O.G.

Mrs. D. R. had four normal pregnancies and deliveries in 1947, 1949, 1950 and 1952; all four children are alive and well.

The fifth baby was expected on 7.1.54. At 3 a.m. on 9.12.53 (i.e. at the end of the 36th week) the patient had a brisk hæmorrhage *per vaginam*. She was sent into hospital as an emergency antepartum hæmorrhage. The patient had lost "a little every month" and there had been a more or less continuous "watery discharge" throughout the pregnancy. A twin pregnancy was discovered and a presumptive diagnosis of placenta prævia was made. There was another heavy loss two days after admission and on that day (December 11) a lower segment Cæsarean section was performed for placenta prævia. Part of the placenta was in the lower segment posteriorly. The twins were born alive but only survived twenty-four hours.

The loss in the puerperium was more than normal and a little offensive. On the tenth day of the puerperium a fairly heavy hæmorrhage occurred. The cervix was inspected and a large cauliflower growth was found surrounded by a base of uninvaded cervical tissue. I was asked to see the patient, confirmed the above findings and at the same time I removed a piece of growth for section. The section was examined by Professor Jethro Gough who expressed an unequivocal opinion that the growth was an adenocarcinoma.

I carried out a Wertheim's hysterectomy on 28.12.53. Several enlarged lymph nodes were found along both external iliac veins and there were some smaller lymph nodes along the internal veins and in both obturator fossæ. The convalescence was uneventful and the patient was discharged on the sixteenth post-operative day.

Fig. 1 shows the uterine body, cervix, appendages and vagina. The extent of the tumour on the vaginal cervix has been shown by everting the vaginal skin. Fig. 2 shows a typical adenocarcinoma with a variable pattern. There is much polymorph infiltration in most of the tumour. Fig. 3 shows a lymph node with a few metastases in its peripheral lymph sinus. One only of the lymph nodes removed showed metastases.

FIG. 1.

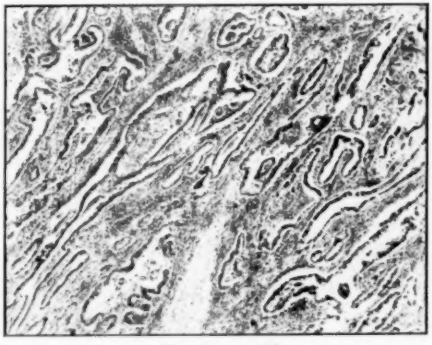

FIG. 2. × 23.

Comment.—The age of the patient is of interest. Maliphant (1949) analysed 1,200 consecutive cases of carcinoma of the cervix treated at the Cardiff Royal Infirmary during the 25-year period 1922–46. At that time the county in which the patient lives was in the catchment area of Cardiff for carcinoma of the cervix. In the youngest age group (20–24) Maliphant reports 5 cases.

The association of cancer of the cervix and pregnancy is reviewed by Munro Kerr and Chassar Moir (1949). The youngest case quoted is aged 23. Munro Kerr and Chassar Moir discuss the

effect of pregnancy on the extension of cancer of the cervix. Doubt is cast on the truth of the statement that cancer of the cervix is more progressive and malignant in pregnancy.

No presentation of a specimen of carcinoma of the cervix in pregnancy would be complete without reference to the cervical tumours closely simulating cancer found on the cervix in pregnancy described by Hill (1948) and Martin and Kenny (1950). In their commentaries, Martin and Kenny focus attention on the ætiology of cancer in general and of cancer in the female tract in particular.

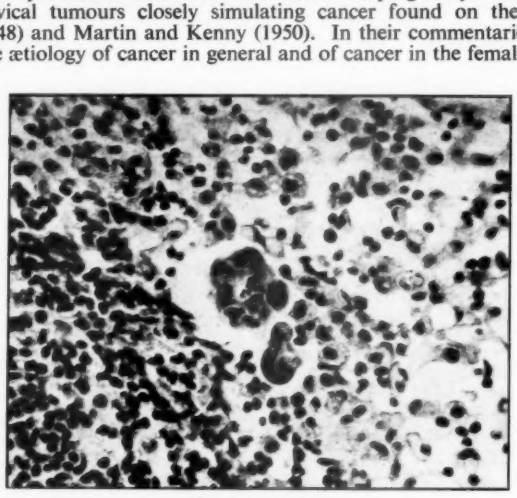

FIG. 3. × 330.

On October 20, 1950, this Section listened to a "Discussion on new ideas about the diagnosis and treatment of placenta prævia". There were lively exchanges of views on vaginal examinations in cases of ante-partum hæmorrhage. There was general agreement that digital exploration of the lower segment would be hazardous. Nevertheless, no harm can come to a case of placenta prævia if the cervix is *gently exposed by a speculum*. Macafee (1945) mentions the gentle use of the speculum. By using a speculum in a case of ante-partum hæmorrhage I saw my first case of carcinoma of the cervix in pregnancy in 1948. The case was dealt with by a Cæsarean Wertheim; mother and child are alive and well.

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Infected Congenital Vaginal Cyst.—ARTHUR CLIFT, F.R.C.S.

History.—Miss M. C., aged 20, complained of an offensive, yellow, vaginal discharge; intermittent over the past four years, more or less continuous for the past four months. She required to wear protection averaging seven sanitary towels daily. She also complained of soreness in the right side of the lower abdomen and found the act of bending limited. She was losing weight. Her periods lasted 11 days every 28, were accompanied by clots and right-sided dysmenorrhœa. There was some frequency of micturition.

On examination.—Heart and lungs and C.N.S. were normal. Abdominal examination: some vague deep tenderness low in the right iliac fossa. She was virgo intacta. Rectal examination revealed a tender cystic mass to the right of the vagina. Under general anæsthesia the intact hymen was incised and on speculum examination the right lateral vaginal wall was found to be distended. About half an ounce of purulent, very offensive, discharge was removed from the posterior vaginal fornix, and on applying pressure to the bulging vaginal wall further pus issued from the right lateral fornix. On bimanual examination a double uterus was discovered. Careful inspection of the vaginal vault failed to reveal any sinus. The cervix was drawn over and fixed in the right vaginal fornix. The cervical canal was dilated but no pus issued from the uterus, thus pyometra was excluded.

Diagnosis.—The possibility of a pelvic abscess pointing in the vagina was considered but there was no supporting history. Apart from the double uterus no abnormality was discovered. The diagnosis of an infected vaginal cyst was therefore reached.

Investigations.—Bacteriological investigation of the vaginal pus revealed a mixed infection, predominantly *B. coli*; tubercle bacilli were absent. E.S.R.—10 mm. in the first hour (Westergren). Hæmoglobin 91% (13·4 grammes/100 ml.). W.B.C. 7,200 (polymorphs. 64%, lymphocytes 34%, monocytes 2%). The menstrual fluids cultured for tuberculosis proved negative. C.S.U. sterile, guinea-pig inoculation—no evidence of tuberculosis. Chest X-ray—no parenchymatous disease. Temperature never rose above 99° F.

As there is a common association between müllerian and wolffian congenital abnormalities the kidneys were investigated and revealed an absence of the right kidney and ureter.

Sodium iodide 13% was introduced into the cyst through a needle and serial X-rays were taken by Dr. Gerald W. Pimblett (Fig. 1).

The abdominal route was chosen for excision of the cyst.

FIG. 1.—An X-ray of the vaginal cyst connected by a sinuous tract to a second cavity—outlined by 13% sodium iodide solution (Courtesy of Dr. Gerald W. Pimblett.)

Operation.—Under general anæsthesia the abdomen was opened. It was confirmed that the right kidney and ureter were absent. The vermiform appendix was found to be congenitally deformed. Double uterus was observed. The right fallopian tube was found to be blind at its lateral end; the left tube patent. Both ovaries were cystic. The right round ligament was clamped and divided and the broad ligament opened. A mass about 1 in. in diameter was first encountered—this was excised and was thought at the time to be remnants of the paroophoron. (Later reflection suggested alternative explanations of this mass: (1) dilatation of wolffian duct, or (2) atrophied kidney.) The cyst was adherent to the cervix and urinary bladder. Removal of the chronic abscess was difficult, and the adherent urinary bladder was unavoidably opened. The bladder was repaired by two purse-string sutures. Difficulty was encountered in introducing a urethral catheter, thought to be due to mechanical blocking of the urethra as the result of suturing the hole in the bladder, and it was therefore thought advisable to drain the bladder suprapubically. The abdomen was closed. A course of penicillin and sulphamezathine was given. Healing was complete within three weeks—vaginal discharge had ceased and normal micturition established.

Pathology.—There was a thick-walled chronic abscess cavity measuring approximately 6 cm. in diameter with an area of vaginal epithelium and a piece of bladder wall. In addition there was a small thick-walled duct situated at the dome of the cyst, close to which was a fistula.

Comments.—In spite of the available clinical, radiological and pathological evidence it is difficult correctly to classify this cyst. A critical analysis of published cases leads one to the conclusion that there are no definite histological findings that can be relied on to determine the ætiology (1–11). In this case both müllerian and wolffian congenital abnormalities were present—a double uterus and absence of the right kidney and ureter.

In favour of the diagnosis of blind vagina (Freund, 1877) was the lateral situation of the cyst to the true vagina; the presence of two uteri and radiologically the apparent connexion of the cyst with a congenital right cervix, uterus and fallopian tube. Sections from various parts of the cyst wall consistently showed a lining of stratified squamous epithelium. The great majority of Gärtner's cysts are lined by a single layer of cubical or columnar epithelium. The fibromuscular wall of the cyst was thick. Against this müllerian hypothesis is the presence of a duct ending in the wall of the vault of the cyst, and in the line of the wolffian duct apparent multiple cysts are seen radiologically. Also no menstrual fluid or blood was obtained from the vaginal cyst.

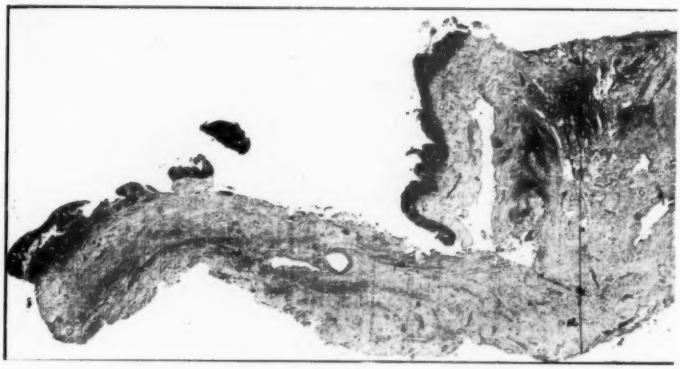

FIG. 2A.

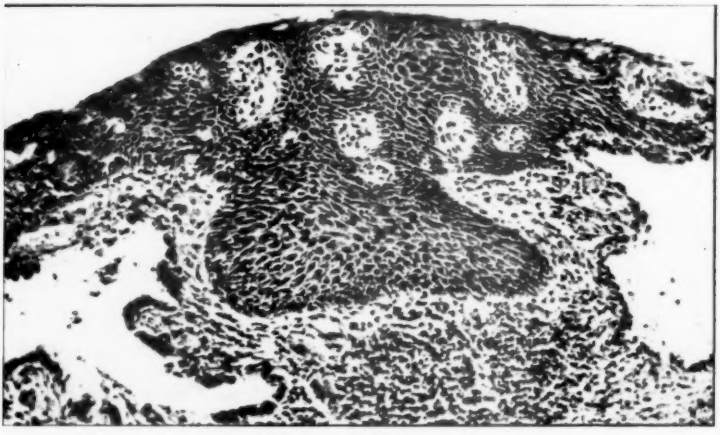

FIG. 2B. × 120.

FIG. 2A and B.—Section of vaginal cyst wall showing smooth muscle and connective tissue. The lining is composed of irregular stratified squamous epithelium, underlying which is an intense chronic inflammatory reaction. A few small ducts lined by columnar epithelium are seen just beneath the epithelium. (Courtesy of Prof. T. Crawford, Drs. A. I. Ross and G. T. Stewart.)

The second possible hypothesis is a Gärtner's cyst—the presence of the duct situated at the dome of the cyst is strongly in favour of this diagnosis. X-ray findings could be interpreted as multiple dilatations in the line of the wolffian duct—the most distal being a Gärtner's cyst. Congenital absence of the right kidney and ureter would also support this theory.

The third possible diagnosis is one of ureterocele, in which case the duct would be ureter—and the proximal cyst part of an otherwise atrophied kidney. In favour of this theory is the fact that the histological features of the duct resemble those of a ureter.

The conclusion is that there is no available irrefutable evidence to lead the author to a definite diagnosis.

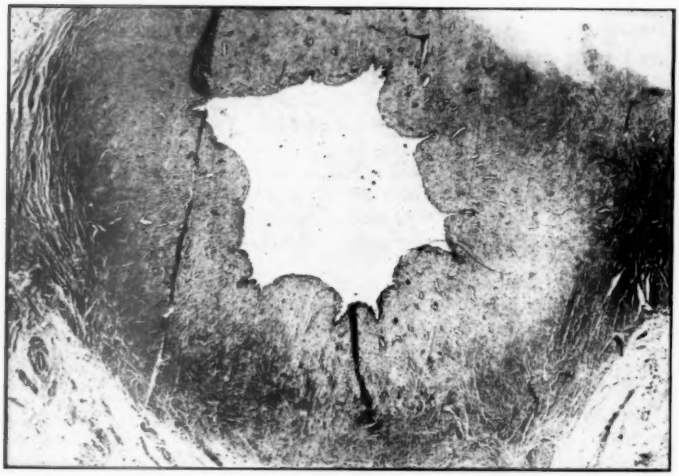

FIG. 3A.

FIG. 3B. × 166.

FIG. 3.—A. Section of the duct ending in the dome of the cyst, showing outer circular and inner longitudinal layers of smooth muscle fibres inside which is a layer of highly vascular connective tissue. The lumen measures 2–3 mm. There is practically no lining epithelium present, but in places there are a few epithelial cells mostly in a single layer; in one place there appears to be stratification suggestive of a transitional type of epithelium.

B. High power showing lining of duct.

(Courtesy of Prof. T. Crawford, Drs. A. I. Ross and G. T. Stewart.)

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A Krukenberg Tumour with No Apparent Primary Growth.—D. H. Lees, F.R.C.S.Ed., M.R.C.O.G.

Mrs. C. T., aged 44, attended the Out-Patient Department of the Jessop Hospital for Women in October 1953, complaining of pain in the left lower abdomen of five months' duration. During that time she had noticed the development of a swelling in the hypogastric region.

Obstetric history.—She had a child aged 6½ and had a miscarriage two and a half years previous to that.

Past history.—In September 1950 this patient had a retrocolic Polya-Hofmeister gastrectomy done for chronic peptic ulceration by Mr. Blacow Yates at the Royal Hospital, Sheffield. The stomach was examined in detail but no evidence of malignancy was found.

On examination.—Her general condition was fair, her hæmoglobin was 82% and her blood pressure 120/70.

A mobile tender mass was felt suprapubically and slightly to the left side and there was free fluid in the peritoneal cavity. On pelvic examination the cervix was slightly open and the uterus itself was displaced forward by a mobile tumour mass which appeared to be ovarian in origin. A diagnosis of ovarian tumour with ascites was made and admission to hospital arranged.

Further pre-operative investigations included a chest skiagram which was normal. Careful examination of both breasts showed no abnormality.

On laparotomy.—Considerable yellow free fluid was found in the peritoneal cavity and bilateral ovarian tumours were disclosed. These were firm and solid with rather a rough surface and typical of Krukenberg tumour. The tumours were free but there was one little nodular area on the peritoneum of the pouch of Douglas. The uterus was slightly enlarged but of normal outline.

Total hysterectomy with removal of both tubes and ovaries was carried out and the nodule from the pouch of Douglas was excised. Following on this a careful survey of the whole abdominal cavity was made. The liver surface, the gall-bladder and the bowel from duodenum to rectum were examined in detail for evidence of a primary growth but nothing was found.

Summary of pathological report (Dr. C. G. Paine).—The ovaries are replaced by solid tumours measuring 95 × 120 × 70 mm. on the right and 120 × 80 × 80 mm. on the left. Both naked eye and histologically these are typical of Krukenberg tumour. In the deeper layers of the endometrium and in the upper part of the cervix, areas of Krukenberg tumour are visible. The nodule from the pelvic floor shows carcinomatous involvement.

Subsequent progress.—The immediate post-operative course was uneventful and in view of the laboratory report she had a course of deep X-ray therapy. On completion of that treatment barium investigation of the alimentary tract was carried out. She had a barium meal and a barium enema but neither screening indicated any abnormality of the bowel. Repeated tests were done for occult blood in the fæces and on two occasions a positive result was obtained.

Comment.—The specimen seems to offer some comment on two open questions regarding these tumours; namely whether they are ever primary, and what is the usual method of spread from the primary to the ovaries. With regard to the first and despite the negative clinical findings in this case the histological sequence bespeaks secondary ovarian involvement. The view is taken that study of the histology must be the criterion and a case like this strengthens the view that a primary growth in the ovary is unlikely. With regard to the method of spread, that was almost certainly lymphatic in this case and the uterine involvement would entail retrograde lymphatic spread from the ovary. It has always been realized that spread from the stomach to the ovary would mean retrograde permeation and the findings here support that opinion.

Section of Surgery

President—Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

[*February* 3, 1954]

DISCUSSION ON PORTAL HYPERTENSION

Mr. Alan H. Hunt:

I feel it right that I should begin by considering the term "portal hypertension". As surgeons, we are largely indebted to Whipple, Rousselot and Blakemore for the practical application of the sum of knowledge in the surgical treatment of patients suffering from portal hypertension, but the term itself was introduced some years before the formation of the spleen clinic at the Presbyterian Hospital, New York. Rousselot, in 1939, attributes its origin to McMichael in 1934, but McMichael uses the expression more or less synonymously with "portal stasis" and "portal congestion" in referring to patients who suffer "elevation of portal pressure" from obstruction to the portal blood-flow. It would appear that the term came into being soon after Eppinger's book in 1920 when congestive splenomegaly was accurately defined and when the conception of the immediate aetiological factor in Banti's disease was shifted from the spleen to the liver or to the portal vein itself; in fact, when intra-hepatic and extra-hepatic portal obstruction began to be elucidated.

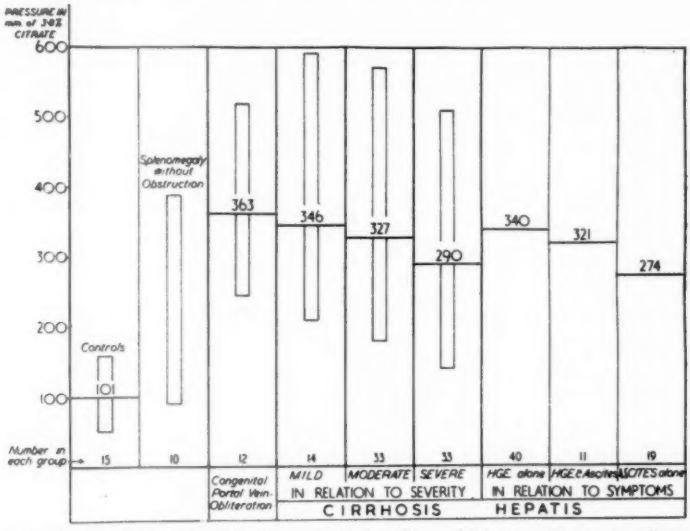

FIG. 1.—Portal venous pressures. Summary of findings: highest and lowest readings in each group, with average levels where applicable.

Fig. 1 shows the pressures that have been encountered during the course of the present study. The normal portal venous pressure has varied between 50 and 160 mm. sodium citrate, with an average at about 100 mm. Patients with congenital portal vein obliteration and cavernoma formation have shown the most constant elevation of portal pressure. Cirrhotic patients have shown greater variation, with the pressure higher in those with mild cirrhosis suffering from hæmorrhage than in those with advanced cirrhosis in whom ascites has been the predominant symptom. The pressure shown by some patients in the latter group has actually been little above normal.

Column 2 of Fig. 1 shows the pressures that have been encountered in cases with primary splenic anæmia in which portal obstruction has been absent. Many are indubitably hypertensive and the hypertension has been due to an excess of blood supply *to* the portal system and not to any damming back of portal blood, as shown by the double venogram (Fig. 2). The picture contrasts markedly with the venograms obtained in portal vein obliteration and in cirrhosis hepatis (Figs. 3, 4 and 5).

Thus primary hypersplenism illustrates clearly that hypertension *per se* is not of such significance as portal stasis. It is necessary to emphasize this point because cases have been reported of Gaucher's

disease and sarcoidosis of liver and spleen in which shunt operations have been done for the relief of portal hypertension; whereas splenectomy alone is sufficient to relieve it, provided there is no stasis.

Portal stasis and the exact position and nature of the causative obstruction should always be demonstrated by portal venography when a shunt is to be made.

The *causes of portal hypertension*, as encountered in a personal series of 142 consecutive cases, are set out in Table I.

TABLE I.—CAUSES OF PORTAL HYPERTENSION (142 CONSECUTIVE CASES)

I.	Extra-hepatic (pre-hepatic):		
	Congenital portal vein obliteration		13
	Thrombosis: Traumatic	1	
	Infective (pylephlebitis)	1	
	Associated with blood disorders:		4
	Myeloid leukæmia	1	
	Lymphosarcoma	1	
	Compression by: Hypernephroma of right kidney	1	
	Displaced left kidney	1	3
	Carcinoma of liver	1	
	Invasion by carcinoma of stomach		2
	Splenic arterio-venous aneurysm		1
			23
II.	Cirrhotic (intra-hepatic)		119
		Total	142

EXTRA-HEPATIC OBSTRUCTION

The treatment of congenital portal vein obliteration (*see* Fig. 3) often presents a difficult problem. Table II sets out the results so far obtained in relation to method of treatment. The condition is particularly distressing because it occurs usually in children. One patient was not operated on and he died of his second hæmorrhage before medical aid could be summoned.

(The treatment of other cases of extra-hepatic obstruction depends very largely on the underlying cause, as may be inferred by studying Table I).

TABLE II.—TREATMENT AND RESULTS OF EXTRA-HEPATIC OBSTRUCTION (TOTAL 23)

	Success	Failure	Death
Congenital obliteration (13)			
1 no operation			1
6 spleno-renal anastomoses	2	4	
5 splenectomies		4	1
3 attempted porta-caval anastomoses	(1)	2	
1 superior mesenteric-inferior vena cava anastomosis		1	
1 inferior mesenteric-inferior vena cava anastomosis		1	
2 proximal gastric resections	2		
5 gastric transections	1	4	
23 operations			
Other spleno-renal anastomoses in traumatic thrombosis		1*	
following pylephlebitis	1		
Other proximal gastric resection in traumatic thrombosis	1*		

(*Same patient)

Methods of Surgical Treatment

Spleno-renal anastomosis is undoubtedly the most satisfactory method of treatment, but in my experience has been successful in only 2 patients out of 6. The remaining four shunts have thrombosed. The tendency for such stomata to become obliterated may be due to the fact that the veins themselves are in a very poor state and that the obliterative process, which originally obstructed the portal vein, tends to continue.

Splenectomy alone should never be done in this group. It had been previously done in 4 out of 5 of these cases, leaving me with four "post-splenectomy bleeders" (Blakemore and Fitzpatrick, 1951). The fifth had splenic vein thrombosis and later died of mesenteric thrombosis.

Porta-caval anastomosis using a cavernomatous channel has been attempted without success on three occasions, one patient remaining remarkably well in spite of the fact that we know that her shunt has thrombosed.

Similarly the use of *superior and inferior mesenteric veins* for the construction of a shunt seems to be valueless, though it may be attempted when one of these veins is large.

"*Interruption*" *operations* (Tanner, 1950) are probably the best method of treatment, failing a

successful spleno-renal anastomosis. I do not wish to trespass on Mr. Tanner's province, but in my experience I find that proximal gastric resection is more satisfactory than proximal gastric transection because of the tendency for hæmorrhages to occur from gastric varices. One patient who has had a proximal gastric resection has been free from symptoms since June 1949. He had had two massive hæmorrhages from his stomach during the earlier part of that year. Another cause of failure of proximal gastric transection is stricture formation, following regurgitant œsophagitis. I find these "interruption" operations tedious and the post-operative course is seldom smooth.

The difficulties in treating this group of patients may be illustrated by the case of a young girl aged 5 with very poor veins. Spleno-renal anastomosis failed. Porta-caval anastomosis was attempted and failed. Proximal gastric transection was carried out; and finally, two years after her first operation the proximal half of her stomach had to be resected as an emergency measure to stop profuse gastric hæmorrhage and save her life. Œsophagoscopy before this last operation had shown that she had no varices above the cardia.

A few significant results in the remaining 10 patients with extra-hepatic obstruction are also given in Table II.

Cirrhosis Hepatis

The probable causes of cirrhosis encountered in this series are set out in Table III. Cases following infective hepatitis were far less common than those in whom the cause was not disclosed, except in the most advanced group, where they were equal in number. Alcohol, as a probable ætiological factor, was encountered comparatively infrequently; whereas inorganic arsenic (given as a therapeutic agency for epilepsy, dermatitis herpetiformis or as a blood tonic) was encountered in 6 patients. All the patients who had suffered from starvation had been prisoners-of-war, 3 in Europe and 2 in Asia.

Table III.—The Probable Causes of Cirrhosis in This Series

Cause undisclosed		52	44%
Infective hepatitis		31	26·1%
Following cholangio-hepatitis		1	
Hepato-lenticular fibrosis (Kinnier Wilson's disease)		1	
Toxic: Alcoholic	7		
Arsenical (inorganic)	6	14	11·8%
Carbon tetrachloride	1		
Biliary: Congenital atresia	3		
An acquired obstruction	5	8	6·7%
Syphilis		3	
Starvation		5	4·2%
Cardiac		2	
Toxæmia of pregnancy (or ?)		2	
		119	

These cirrhotic patients have been divided after the suggestion of Whipple (1945) into three groups, the mild, the moderate and the severe.

The *mild* may be defined as those in whom the cirrhotic process is not reflected in any abnormality of biochemical function of the liver, with the possible exception of the pseudocholinesterase, and in whom considerable clinical experience is required to recognize the fact that the liver is in any way diseased.

The *moderate* are those patients in whom there is clinical evidence of liver disease and appreciable deterioration of liver function as indicated by tests, but in whom the serum albumin level is above 3·2 grammes per 100 c.c. I am no slave to a figure, but it does appear that this is a critical level so far as prognosis is concerned (Blakemore, 1952). These moderately cirrhotic patients almost always survive diversion of their portal blood (Blakemore, 1951).

The *severe* cirrhotics are those in an advanced state of liver deterioration, with serum albumin levels of less than 3·2 grammes per 100 c.c., or in whom there is some complicating factor making them extremely ill and virtually in the terminal stages of their disease.

It should be noted in passing that active thrombosis of the portal vein was proved to be present in 15 (or 12·6%) of these 119 patients with cirrhosis. It was found in 6 out of the 23 patients with extra-hepatic obstruction, giving a percentage in that group of 26%, excluding congenital portal vein obliteration.

In the treatment of cirrhosis hepatis I value greatly the co-operation of the physicians. Team-work is a necessity. There is no competition between medical and surgical treatment.

The indications for operation in cases of cirrhosis hepatis are: (1) Hæmorrhage. Hæmorrhage renders operation essential and cannot otherwise be dealt with successfully. (2) Ascites. This is not necessarily a contra-indication to operation when it is associated with hæmorrhage, provided the immediate risks of operation are not excessive. Ascites alone may on rare occasions be an indication for surgical treatment, but this should be contemplated only after failure of at least three months' intensive and co-operative medical treatment. (3) Other indications. From time to time jaundice or splenic anæmia may in themselves be causes for operation.

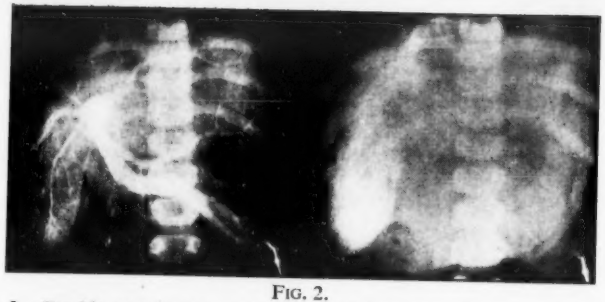

FIG. 2.

FIG. 2.—Double portal venogram in a case of Gaucher's disease. Portal venous pressure 270 mm. water. To show absence of obstruction to portal flow and no stasis, in spite of the hypertension (cf. Figs. 3, 4, and 5).

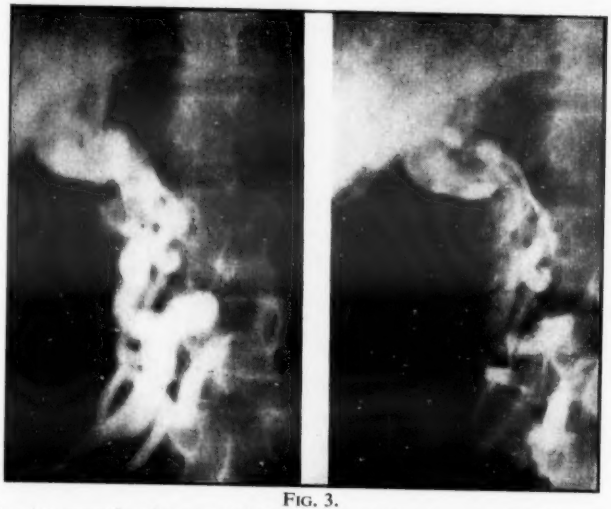

FIG. 3.

FIG. 3.—An example of congenital portal vein obliteration, the double venogram showing stasis.

FIG. 5.—Double portal venogram in a case of cirrhosis hepatis to show sluggish

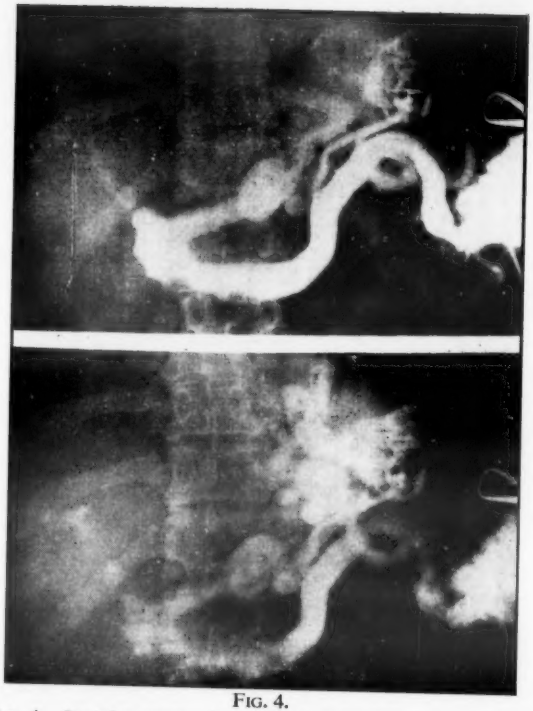

FIG. 4.

FIG. 4.—Portal venogram in a case of cirrhosis hepatis with portal vein thrombosis. Portal venous pressure 350 mm. The stasis contrasts markedly with Fig. 2.

Methods

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FIG. 6.—Double portal venogram in a case of cirrhosis hepatis to show sluggish flow in the portal vein. Portal venous pressure 350 mm. water. Compare with Fig. 2. (cf. Figs. 3, 4, and 5).

EE

Methods of Surgical Treatment

Splenectomy alone is very rarely indicated. Only 2 patients with cirrhosis benefited from the operation. In the whole series of 142 patients it has been done without effect, either by someone else or by me, in 23 patients.

The most satisfactory method of preventing hæmorrhage in cases of cirrhosis hepatis is by relieving the portal stasis and hypertension by the construction of portal-systemic venous anastomosis and the best type of shunt is *end-to-side porta-caval anastomosis.* Most people who have studied this subject agree that this is so. The direction of flow is not altered and a good big stoma can be made. The average size of more than 40 such shunts has been 17 mm. in diameter.

The side-to-side (or "in continuity") porta-caval anastomosis I have done three times. It is a more dangerous procedure because it allows back-flow of hepatic arterial blood from the liver, thereby depriving the liver of even more than its portal blood supply.

Spleno-renal anastomosis, preferably end-to-side (but if that is not possible, end-to-end) should be done in two circumstances: (1) when there is a very large and over-active spleen with leucopenia (of less than 2,500 W.B.C.) and thrombocytopenia (of less than 75,000 platelets); and (2) when the portal vein is thrombosed and cannot be used for a shunt (Fig. 4). However, it is sometimes possible to construct shunts using partially thrombosed portal or splenic vein. I have 5 successful cases in which the clot has been removed with the aid of a Volkmann's spoon (Hunt and Whittard, 1954). Here again it is necessary to emphasize the value of portal venography and the inadvisability of removing the spleen for want of proper elucidation of each patient.

Other *exceptional technical considerations* may compel one to make a spleno-renal anastomosis rather than a porta-caval, such as excessively large collateral anastomotic channels in the region of the portal vein: and, vice versa, a porta-caval instead of a spleno-renal when the splenic vein is so arranged anatomically as to make a shunt impossible. (In this instance, of course, a preliminary splenectomy is inevitable.)

Operative Approach

One must be prepared at operation to switch from one approach to the other, and this may be done by having the patient in the dorsal position, with elbows up and hands on opposite shoulders—as it were, in the dorsal hornpipe position. Exploration and venography are done through the abdominal part of the incision for the probable operation. The incision is then extended up into the chest, after the state of the portal venous tree has been demonstrated. If the planned operation is shown to be impossible, the incision can be extended over to the other side with the minimum of disturbance.

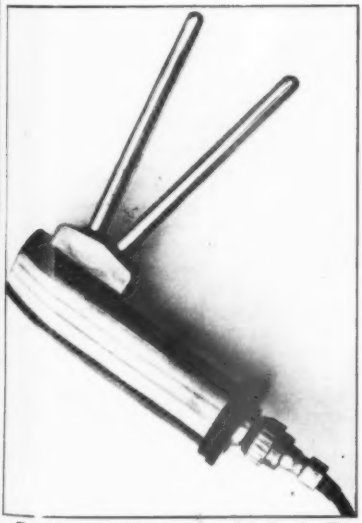

FIG. 6.—Double probe-pointed scintillation detector for use in estimating the speed of flow in the portal vein.

Speed of Flow in Portal Vessels

Patients with portal hypertension sometimes have very large umbilical veins, as shown on the venogram (Fig. 5). The vein in this case was 15 mm. in diameter. It has been asserted that such a vein would carry off at least as much blood as an artificial portal-systemic venous anastomosis. The double venogram, however, demonstrates clearly the stagnation that occurs in these collateral anastomotic vessels. In this case we measured the speeds of flow in the various channels. In the portal vein it was 4·5 cm. per second before porta-caval anastomosis and 8·0 afterwards, this being the normal speed. In the umbilical vein, however, it was 1·4 cm. per second. The porta-caval stoma was 2 mm. larger in diameter than the umbilical vein. The pressure before anastomosis was 250 mm. H_2O and after, 125. The shunt operation, it appears, drains the portal reservoir from the bottom, whereas the collateral vessels, however large they may be, do no more than top it off.

The instrument that we have used for measuring the speeds in these vessels has been devised and worked for me by Professor W. V. Mayneord and Dr. E. H. Belcher (Fig. 6). It is a double probe-pointed scintillation detector coupled to a photo-multiplier tube and so to a pen recorder. We refer to this apparatus as the Winston, for obvious reasons. The tips of the fingers are 7·5 cm. apart. A minute quantity of radio-active sodium is injected peripherally and it can be detected with the Winston as it passes each finger of the instrument.

The results of the treatment of cirrhosis hepatis, in relation (*a*) to the method of treatment and (*b*) to the extent of the disease, are set out in Tables IV, V and VI. Only significant operations are considered and unsuccessful splenectomies, explorations, &c., have been omitted.

TABLE IV.—TREATMENT AND RESULTS OF MILD CIRRHOSIS (TOTAL 19)

		Success	Failure	Late death
5	without operation for portal stasis	4		1
1	splenectomy			1
5	porta-caval anastomoses	5		
8	spleno-renal anastomoses	7		1

Results

12 out of 13 shunted cases restored to normal health, operative mortality nil.

TABLE V.—TREATMENT AND RESULTS OF MODERATE CIRRHOSIS (TOTAL 43)

		Success	Failure	Early death	Late death
Up to December 1951 (16)					
4	without operation for portal stasis		2	1	1
4	porta-caval anastomoses	2		2	
6	spleno-renal anastomoses	3	1*	1	1
1	gastro-œsophageal resection			1*	
1	biliary operation		1†		
Since January 1952 (27)					
7	without operation for portal stasis	4	2	1	
15	porta-caval anastomoses	13	1		1
2	spleno-renal anastomoses	2†			
2	hepatic arterial ligatures	2			
1	gastric transection			1	
1	biliary operation	1			
1	splenectomy	1			

Results

Up to December 1951: 5 of 10 shunted cases very well, 3 operative deaths.
Since January 1952: 15 out of 17 shunted cases successful (88·2%), no operative death.
(* and † same patients)

TABLE VI.—TREATMENT OF VERY SEVERE CIRRHOSIS (TOTAL 57)

To December 1951, 26 cases, all dead, whatever the treatment.
Since January 1952, 31 cases.

		Success	Failure	Death
12	no operation	1	1	10
6	porta-caval anastomoses	3		3
3	spleno-renal anastomoses	2		1
9	hepatic arterial ligatures			9
1	biliary			1
31		6 (20%)		

CAUSES OF DEATH, WITH OR WITHOUT OPERATION

Liver failure in	39
Hæmorrhage *per se* (3 post-operative with heparin)	5
Thrombosis and liver failure	2
Other causes	4
	50

From amongst this mass of detail we may conclude that porta-caval (or spleno-renal) anastomosis is now a very successful method of treatment with a low operative mortality in cases of mild and moderate cirrhosis; and that even the desperately ill patients in the very severe group are not necessarily hopeless operative risks.

Operation for hæmorrhage should, therefore, be done as early in the course of the disease as possible and while the liver is still functioning well. Delay may lead to unsurmountable liver damage, apart from the ever-increasing risks of death from hæmorrhage itself.

The indication for operation was, (*a*) in the mild cases, always hæmorrhage, (*b*) in the moderate, usually hæmorrhage, and occasionally ascites, and (*c*) in the severe, usually hæmorrhage and ascites. Altogether 13 successful shunt operations have been done on patients who were grossly ascitic at the time of operation.

Late results.—It is not yet possible to say what the final outcome of these rather drastic operative measures will be. Our present method of follow-up was standardized in 1952 and I have made an

attempt to assess how the patients are and what has happened to the liver and the blood in a group of patients operated on between September 1952 and July 1953. "Success" infers that they have not bled again and that they have been able to return to normal activities without any trace of ascites. The majority have been able to do full work. For example, one patient has returned to the oilfields in Peru, one to take command of a new ocean-going tanker, one to his farm in Kenya; others to work in factories and to normal farm labouring; and to ordinary sport such as football and horse-riding. Their general health, in fact, has been excellent. Spider nævi have often faded or disappeared and caput medusæ have collapsed.

Following porta-caval anastomosis the spleen has always shrunk and become less active. The liver, to palpation and percussion, has shown little change; but has appeared, from the patient's point of view, to function very much better. Ascites has disappeared, even in one patient where it had been forming at the rate of 2,600 c.c. per day before spleno-renal anastomosis. Œsophageal varices may still be demonstrable but can be made to disappear (on barium swallow) by the slight increase in intrathoracic pressure caused by expiration.

The improvement in hæmoglobin and pseudocholinesterase shown in Table VII has been comparable with the clinical improvement. The serum albumin has changed little though the change has been for the better. The white blood cell and platelet counts are in keeping with the reduction in size of the spleen or, in the case of spleno-renal anastomosis, with the removal of the spleen.

TABLE VII.—PATHOLOGICAL ASSESSMENT FOLLOWING CLINICALLY SUCCESSFUL SHUNT OPERATIONS, SEPTEMBER 1952–JULY 1953 (Average figures for the two groups)

	Porta-caval anastomosis (14)	Spleno-renal anastomosis (4)
Hæmoglobin	+20%	+16%
White blood cells	+2,000	+5,000
Platelets	Increased	Much increased
Serum albumin	+0·1 grammes%	+0·8 grammes%
Pseudocholinesterase (Normal: 50–120 units)	+8 units	+19 units

I do not necessarily infer by these results that the liver is capable of regenerating. I have not detected enlargement of the liver following shunt operations. I do, however, suggest that the relief of portal congestion enables the liver, such as it is, to function better and without the devastating set-backs of recurrent hæmorrhages.

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Mr. Norman C. Tanner: Portal hypertension is *not* a frequent cause of bleeding; it is very important because of its high mortality rate. In our clinic at St. James's Hospital, out of our last 1,353 incidents of massive hæmorrhage and melæna, portal hypertension was responsible for 41. The mortality figures for bleeding œsophageal varices and excluding other forms of bleeding due to portal hypertension were—1943-47: 10 admissions, 8 died, 80% mortality; 1948-52: 16 admissions, 5 died, 31% mortality.

In addition a very high percentage of the survivors of bleeding died within eighteen to twenty-four months of bleeding.

Bleeding in cases of portal hypertension does not often arise in the purely hypertensive part of the alimentary tract, but rather in those parts where there is an excessive collateral circulation between the hypertensive portal and normotensive systemic or caval veins. Colon carcinoma and duodenal ulcers bleed little more in patients with portal hypertension than in normal sufferers, though the nearer an ulcer is to the upper stomach or to the anus the greater is the tendency to bleed. Although bleeding piles are, at times, troublesome and proctoscopy may reveal somewhat varicose rectal veins in cases of portal or inferior mesenteric vein obstruction, bleeding from this source rarely threatens life. The chief dangers arise from the varicose veins which develop as a result of the excessive circulation between the vasa brevia and left gastric branches of the portal and the azygos and hemiazygos veins of the systemic circulation. These veins extend from the upper part of the œsophagus to the cardia and sometimes they can be seen in the upper stomach. Varicosities in the lower stomach usually result

from inequalities in pressure between different parts of the portal system, for example in splenic vein obstruction most of the varicosities are between the branches draining into the distal part of the splenic vein and those into the left gastric vein. The gastro-epiploic arch becomes varicose and on gastroscopy varicosities may be seen in the lower stomach. In most cases, hæmorrhage originates in small erosions over the varices.

The diagnosis of portal hypertension is usually clinical. A number of the cases may have a dyspeptic history apart from those with associated peptic ulceration.

At St. James's Hospital we perform early gastroscopy on most of our cases of massive gastro-duodenal bleeding of uncertain origin. If air is gently blown into the œsophagus during the withdrawal of the instrument, excellent though sometimes fleeting views of the œsophagus may be obtained. So far we know of no case where gastroscopy provoked or increased bleeding.

Death may result from anæmia due to excessive bleeding, but not infrequently it is due to hepatic failure precipitated by the recurrent hæmorrhages. Death frequently follows bleeding in patients who would otherwise have had adequate liver function to preserve them for many years. Prevention of death from bleeding would therefore lead to a great saving of useful life.

Methods of Treatment

Medical management.—The swallowing of coagulants, e.g. thrombin, appears to have little effect. The local application of oxycel gauze is difficult and uncertain. The mainstay of medical management has been morphia and blood replacement. The greatest advance in medical management is undoubtedly the introduction of the intra-œsophageal balloon (Rowntree *et al.*, 1947) and this is one of the reasons for the fall in mortality. At first a double balloon on a double or treble lumen tube (Sengstaken) was used. One of the lumina is used for feeding the patient and for periodical aspiration to confirm that bleeding has ceased. The second is used to blow up the balloons. One of these was inflated in the stomach and retained the tube in position, and the second balloon was inflated in the lower œsophagus. The tube was kept in position by gentle traction with a weight on a pulley, or as Wallace *et al.* (1953) recommend by making a wire mask to fix on the face, to which the tube can be fixed under slight tension. To prevent gradual deflation of the balloons, the tube connected to them may be attached to a sphygmomanometer and a steady pressure of 30–40 mm.Hg maintained. The object of the intra-œsophageal balloon is to obstruct the passage between portal and œsophageal veins, so that the pressure in the œsophageal veins may drop to the level of the systemic veins, and bleeding from the varices will stop more readily.

Various troubles have occurred from the use of the balloon. Ulceration from pressure of the tube, particularly round the nares, is common. Asphyxia has occurred from the distended balloon being drawn up into the pharynx. We have lately followed Linton's suggestion (1953) to use traction on only one balloon—the intra-gastric—and to omit the intra-œsophageal balloon. This presses on the lower end of the varices where they project into the stomach, and cuts off the high portal pressure from the œsophageal varices.

The balloon, in one form or another, has been very effective. The main disappointment from the method is, however, that the mortality of bleeding varices remains high, for bleeding often recurs time and again after the tube is removed. It has, however, probably reduced the mortality from 75–80% right down to about 50% (Reynolds *et al.*, 1952) and is partly responsible for reducing our mortality from 80% to under half that figure.

Surgical methods have been used both in the acute phase, and in the interval between hæmorrhages to prevent recurrence of bleeding.

In my own series I have found the following three methods of negligible value either in treatment or prophylaxis: (1) Ligature or injection of the coronary vein at laparotomy. (2) Trans-œsophagoscopic injection of œsophageal veins or peri-œsophageal tissue with sclerosants. (3) Ligature of splenic artery or splenectomy.

Ligation of the hepatic artery has been suggested in treatment of acute bleeding. Its mortality is probably too high to justify it. Ligature of the hepatic and splenic arteries was used in the acute phase of bleeding œsophageal varices in 3 cases by Miller and Owen (1953). Bleeding stopped during the operation in each case, but 1 patient died after it and bleeding recurred in the 2 survivors seven days and five months respectively after operation.

I have always been attracted by the idea of making a complete surgical division between the veins of the portal and the azygos systems, below the cardia. As it is convenient if this operation can be done at an abdominal exploration for hæmatemesis, I first used the operation which I described to this Section in 1949 (Tanner, 1950) and which I called trans-gastric porta-azygos disconnexion, in which the stomach is transected and resutured after dividing all the vasa brevia and branches of the left gastric vein which drain the stomach above the line of transection. The splenic and left gastric arteries were also tied to diminish the volume of portal venous blood.

Unfortunately, some 3 or 4 of the cases eventually bled again. It was found by post-mortem vein injection methods that there was no appreciable flow across the gastric suture line eighteen months after transection and resuture, but venous connexions between the œsophageal veins and inferior phrenic veins around the cardia kept the pressure up in the varices, presumably because the inferior

phrenic veins had become hypertensive. Therefore I modified the operation and since 1951 have carried out what is now a subcardiac porta-azygos disconnexion as follows: By an abdominothoracic approach the lower 5 cm. of œsophagus, the cardia, and upper 5 cm. of greater and lesser curve fo

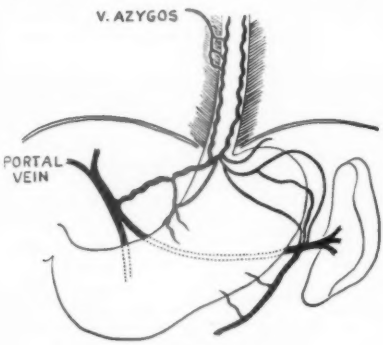

FIG. 1A.

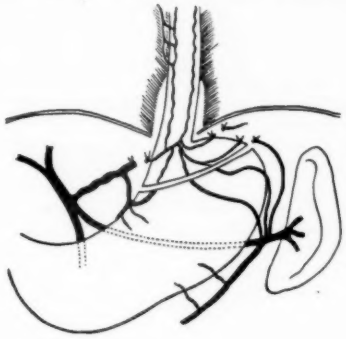

FIG. 1B.

FIG. 1.—A, A diagram of the collateral circulation between the portal and azygos veins. B, The site of venous ligature and of gastric transection in subcardiac porta-azygos disconnexion.

FIG. 2.—An X-ray showing the site of resuture after subcardiac porta-azygos disconnexion.

stomach are entirely freed from all external vascular connexions. The stomach is then completely transected 5 cm. below the cardia and firmly resutured (Fig. 1). There is just enough blood supply from the œsophagus to nourish the small upper gastric segment. An attempt is made to preserve the hepatic branch of the anterior, and cœliac branch of the posterior vagus, but if the vagus has to be completely severed I add a Ramstedt type of pylorotomy. This operation appears to have effected a considerable improvement in cases of acute bleeding and in the interval just after a large hæmorrhage (Fig. 2).

Of 4 cases of low gastric transection followed up—all non-alcoholic cirrhosis—3 had recurrent massive bleeding at four, five and eighteen months, and 1 remains well after three and a half years. Of 8 of the newer subcardiac transections, 5 remain well at three, ten, twelve, eighteen and twenty-one months, 1 died of bleeding but also had a chronic gastric ulcer, and 2 had minor hæmorrhages—a significant improvement on the first series. To sum up—three-quarters of the low transections bled again within eighteen months—all severely, and of the 8 subcardiac transections 38% have gone over a year without further bleeding and only one severe bleeding has occurred.

Professor R. Milnes Walker remarks that the trans-gastric porta-azygos disconnexion is often difficult on account of adhesions and has recommended a variant—transection of the lower œsophagus.

Another direct method of dealing with bleeding varices is resection of the lower œsophagus, but this is a more risky procedure and I do not know if it is much more permanent in effect than porta-azygos disconnexion. Ligature methods are advocated by Boerema (1949) and Crile (1953) who treat varices rather as they would hæmorrhoids. Using a transthoracic approach through the eighth rib bed, an incision 2.5 cm. long is made into the œsophagus, 5 cm. above the cardia. On holding the gullet open three groups of varices are seen which project into the stomach. Each varix is obliterated by a running suture, and Crile recommends that the suture be continued down until gastric mucosa is reached and as high in the gullet as can be reached through the incision. Crile has used the method in 9 cases of extra-hepatic portal bed block without mortality, and only 2 had bled again. This method of treatment

was first advocated by Boerema and has the advantage of having a much lower mortality than œsophago-gastric resection. On the other hand, in cirrhotic cases its effect appears to be only temporary, for Linton found that bleeding recurred in 5 out of 14 Boerema-Crile operations between two weeks and five months after operation. It is remarkable how readily hypertension in varices recurs if any vascular connexion remains between the coronary and azygos veins and so this operation, which leaves many minor œsophageal veins untouched, will have only a temporary effect. It is probably only to be regarded as an emergency procedure.

As an interval method, perhaps the most rational method is to treat the case by some form of porta-caval venous shunt. This may greatly reduce the size of gastric varices.

My present impression is that the patient with bleeding varices should first be treated by traction on a subcardiac balloon and if bleeding recurs twice on removal of the balloon and after a minimum of forty-eight hours, then surgical interference is required. The operation I have used to stop bleeding is a subcardiac porta-azygos disconnexion, though I will agree that in common with many other operations for portal hypertension it is often not technically easy to carry out. It is possible that this in turn should be followed by a porta-caval anastomosis in suitable cases. Certainly if the Boerema-Crile form of ligature of the varices is used to stop the bleeding, I am of the opinion that eventual recurrence is so certain that an interval porta-caval anastomosis is very desirable in cirrhotic cases.

I have always held it is unwise to publish new and incompletely worked out operations prematurely. This is certainly the case when dealing with conditions such as peptic ulceration in which reasonably safe operations are already available. When considering conditions like hæmorrhage from œsophageal varices, in which 70% of the patients are dead within a year of the first bleeding (Ratnoff and Patek, 1942), I believe that the rule can be relaxed in order that we can all keep abreast of the most recent ideas and so hasten the time when we can offer these patients a better chance of long survival.

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Dr. E. R. Cullinan: Brilliant advances have been made in the surgical treatment of portal hypertension since the year 1887 when Talma of Utrecht (1898) first suggested that an attempt be made to develop a collateral circulation between the portal and systemic venous systems by creating adhesions between the two layers of the peritoneum. Van den Meulen tried the operation for him in the following year; the patient died immediately. Even to-day the new surgical skills are still hazardous, and one is faced with two difficult questions: which cases are suitable for surgical treatment, and why?

When portal hypertension results from an extra-hepatic block of the portal vein, and particularly if the patient is having dangerous and repeated hæmorrhages from œsophageal varices, indications for a surgical attack are often clear, because otherwise the effects of the block may be immutable. When portal hypertension results from intra-hepatic portal obstruction, that is to say from cirrhosis, the decision is more difficult. In some cases response to medical treatment alone may be good; in others, the degree of liver cell damage may be so great that an operation is more dangerous than the disease. Cirrhosis of the liver is the end-result of a number of different processes, and although some of these are ill-understood, much help in determining the best type of treatment can be had by considering the antecedent history of individual cases. I do not, of course, refer to well-recognized types such as pigment, biliary or cardiac cirrhoses, but to the so-called portal cirrhosis of Laennec. This includes two main clinical groups with quite different histories:

The first group is cirrhosis resulting from long-standing subacute necrosis of the liver, which may start as infective hepatitis or inoculation hepatitis, or again for no obvious reason. In the earlier phases of the disease there is clinical and pathological evidence of single, spaced, violent assaults on the liver cells. The outstanding clinical feature is jaundice, slight or deep, which may wax and wane for weeks or years, or come in attacks at intervals varying from weeks to years. The disease may end in recovery or in hepatic failure and death, but should it extend over many years it often develops into a condition indistinguishable from portal cirrhosis. This group is far less common than the second but is important to recognize because of the grave dangers of surgical interference during the phases of active liver cell damage in which one usually sees it; that is, when the patient is jaundiced and the hepatic floculation tests are grossly abnormal. In a series of 20 proven cases which I once collected (1936), admittedly before we knew about prothrombin levels and the like, 12 had had a laparotomy because of uncertainty of diagnosis. Of these, 7 died within five days of operation: 2 following severe hæmorrhage but 5 from unexplained liver failure.

The second group is the more usual, and has quite a different history. The early stages are quiet and long. The liver may be enlarged for years, but there may be no symptoms other than perhaps

vague gastro-intestinal complaints and, especially if the patient is an alcoholic, of dyspepsia and tell-tale morning nausea. Clinical evidence of liver cell damage is often absent until late stages of the disease. Jaundice is rare and is often a grave omen of impending hepatic failure. The picture, as we generally see it, is when the disease is far advanced and portal hypertension is manifest; with dilated collateral vessels and splenomegaly, and perhaps hæmorrhage and ascites.

The ætiology of many of the cases in this second group remains quite obscure. It is known that portal cirrhosis may very occasionally be a late sequel of infective hepatitis, but that this is often so, apart from subacute necrosis which I have already mentioned, is extremely difficult to believe. Granted that an attack of infective hepatitis without jaundice may have consequences as serious as an overt attack, surely one would expect a past history of jaundice in patients suffering from cirrhosis more often than in the general population of the same age groups. Yet, this is not one's experience. Zieve *et al.* (1953) studied a number of men who had had viral hepatitis four to six years prior to examination and a number of controls—58 out of 60 needle biopsies on the post-hepatitis cases were normal, and 12 out of 16 controls. They concluded that the few abnormals in either group were most likely related to excessive alcohol consumption with the exception of two individuals with non-specific granulomata.

Some adult patients have a history of long-standing consumption of alcohol, particularly of spirits. This is less common to-day in this country than it was fifty years ago as shown by the Registrar-General's figures for the crude annual death-rate from cirrhosis of the liver in the civilian population of England and Wales. In 1898 it was over 130 per million living. In 1947 the figure had fallen to just over 20. Nevertheless, it is still often seen and about half my own cases give such a history. Nutritional lack is an important factor in the production of some cases at least of human cirrhosis, although its exact role is uncertain. It probably plays an important part in the genesis of "alcoholic" cirrhosis, where the intake of food is low from loss of appetite and the absorption from the gut is presumably poor from inflammatory changes. One rarely finds cirrhosis in an alcoholic whose appetite and intake of food have remained unimpaired.

Prognosis of cirrhosis of the liver is always serious, but a defeatist attitude in the medical treatment of the disease is unwarranted. The damaged liver has remarkable powers of recovery. The most satisfactory cases are those who have a history of alcoholism. As soon as these patients stop taking alcohol and eat an adequate diet, the degree of improvement, even when portal hypertension is well established, is often startling. Abstinence must be absolute, and for life. This is less difficult to achieve than it sounds. Many of the patients are heavy social drinkers rather than compulsive drinkers, and encouragement, sympathy and a frank explanation of the choice between good health and a long, dreary illness will usually persuade them to stop at once and for ever. Adequate feeding, with a diet high in calories, rich in protein, carbohydrates and vitamins especially the B complex, and moderate in fat, is essential. The patients often have a poor appetite, and success will depend much on encouragement and the skill of the caterer. This is not the place to discuss the medical treatment in detail, but it should be added that intercurrent infections must be treated promptly and that morphine and barbiturates should, as far as possible, be avoided.

Hæmorrhage from turgid œsophageal varices may be the first symptom of cirrhosis of the liver. It is a sinister happening. Recurrence is common. Patek and others (1948) found that approximately 50% of patients who had had such hæmorrhage died within one year after the first bleeding. It is impossible to control these hæmorrhages by medical means and if they are repeated and dangerous, this would seem to me to be the important indication for surgical treatment. In adult cirrhotics, hæmorrhage may precede ascites, which indeed it may precipitate. My impression is, that once ascites has developed, hæmorrhage is less frequent. Whereas the physician has little to contribute to the control of hæmorrhage in portal cirrhosis, he has much to offer in the treatment of ascites.

The cause of ascites in cirrhosis is complex, and several factors are involved. Prentice and others (1952) have shown by tracer techniques that ascitic fluid is not a trapped reservoir, but a continually circulating pool, 40–80% of which enters or leaves the peritoneal cavity each hour. The transudate results not only from increased portal venous pressure, but also from a fall in the plasma colloid osmotic pressure resulting from the low level of albumin in the blood thus decreasing the capacity for reabsorption of the fluid. In addition, as ascites forms, most of the sodium taken by mouth in excess of that lost through the skin and fæces, which is normally excreted in the urine, is deposited in the ascitic fluid (Eisenmenger, 1952). Also, an increase of antidiuretic hormone causes the patients to pass small amounts of urine of high specific gravity. The retention of sodium and water increases both the inflow and the load.

Medical treatment is aimed at correcting three of these factors. The level of blood albumin is raised by improving nutrition with a high protein diet, supplemented with sodium-free milk protein products. Sodium intake is restricted to not more than 0·5 gramme a day. This is done by adding no salt to food during cooking or at table, forbidding porridge and using salt-free butter or kosher margarine, and salt-free bread. Ion-exchange resins should help, but often nauseate the patient and I think are better avoided. Fluids are unrestricted. Diuresis is aided by twice-weekly intramuscular injections of a mercurial diuretic, varying the brand with advantage. I do not give ammonium chloride, partly because I feel it upsets the patient's capricious appetite, and partly because alarming symptoms of impending hepatic failure have been described following its use (Phillips *et al.*, 1952).

When treatment begins, one or two paracenteses may be necessary, but their number should be reduced to an absolute minimum. Far from effecting a cure, the removal of large quantities of protein from the body (one litre of ascitic fluid corresponds to approximately 200 c.c. of blood plasma) may cause considerable worsening in the already damaged liver. The treatment may take two or three months, but as nutrition improves and the level of serum albumin rises, salt restriction can gradually be relaxed and sometimes abandoned. Results are often remarkable. I have, at the moment, a patient whose ascites disappeared after one month's treatment on this regime, who had had fifty-one paracenteses in the previous eleven months. The serum albumin has risen in two and a half months from 3·2 grammes per 100 mils. to 4·1 grammes.

As Mr. Hunt has said, the present indication for surgical treatment in portal hypertension seems to be repeated and dangerous hæmorrhage from œsophageal varices. In general, suitability for surgery depends on lack of severe and active damage of the parenchymal liver cells. The assessment of this depends as much on clinical appraisal as on pathological tests. For instance, I would not care to chance the dangers of a major surgical assault based solely on the results of, say, the pseudocholinesterase, good though the test may be.

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Professor L. J. Witts: The surgery of portal hypertension is, in fact, the surgery of œsophageal varices, as ascites is rarely an indication for operation. There are only two methods of attacking œsophageal varices: the one is to lower the portal pressure by shunting the blood into the systemic circulation, the other is to try to divert the portal blood into less dangerous anastomotic channels by blocking the gastro-œsophageal anastomoses. These two approaches are not antagonistic and both may be required in the same case.

Professor R. Milnes Walker: There are only two contributions I wish to make: the first is to emphasize the value of portal venography by intrasplenic injection in giving information before operation regarding the site of obstruction and which veins are available for an anastomosis. We carry it out in every case as a routine and have had no serious complications in about 30 cases.

Secondly, I would stress the importance of the right thoraco-abdominal incision in order to approach the portal vein. I believe that the best anastomosis is an end-to-side porta-caval anastomosis and this approach gives much the best access. During the last four years I have used it in 29 operations of end-to-side porta-caval anastomosis. The results have been most encouraging; 2 patients died during the early post-operative period of hepatic failure and 1 has died since from further hæmorrhage. In only 2 others has there been any further bleeding.

In patients in whom no vein is available for an anastomosis the problem is much more difficult. Where the danger of hæmorrhage is great I carry out a gastric or œsophageal transection through the left thorax, in some cases cutting the stomach or lower œsophagus across completely and resuturing it, in others dividing the muscle of the lower œsophagus longitudinally and transecting only the mucosa and submucosa which contain the large varices. 19 of these operations have been performed without mortality in hospital, 2 patients have subsequently died of further bleeding, 7 are alive but hæmorrhage has recurred, 10 have remained free from hæmorrhage but in 2 the interval since operation is less than six months. Though these results are not encouraging I regard the operation as worth while as it carries little risk and the danger of leaving these patients is great.

Mr. Alan Hunt, in discussion: In considering Mr. Tanner's paper I wish to mention that I have tried compressing the lower end of the œsophagus with the Sengstaken balloon on a number of occasions and I have found it a very difficult method to apply successfully and very uncomfortable for the patient. Bleeding often starts when the balloon is removed. I have done Crile's operation (1953) once to stop bleeding which had been going on almost continuously for two months in spite of the use of the balloon. It was completely successful and enabled porta-caval anastomosis to be done a fortnight later. Dr. Cullinan says that about half his cirrhotic patients were alcoholics and responded extremely well to medical treatment. It is, as a rule, only those patients who fail to respond to medical treatment who are referred to the surgeon. I agree with Professor Witts that ascites by itself is rarely an indication for operation. One is driven to operating on some of these unfortunate patients because it may be their only slender chance of a tolerable life. I am interested in Professor Milnes Walker's remarks on pre-operative portal venography. I do not consider the method as safe as venography obtained on the operating table, as there may be some risk of damage to, or hæmorrhage from, the spleen, apart from accidental puncture of other organs.

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Section of Ophthalmology

President—HUMPHREY NEAME, F.R.C.S.

[*February* 11, 1954]

DISCUSSION: TOXOPLASMOSIS

Professor R. J. V. Pulvertaft showed a film illustrating the behaviour of toxoplasma in vertebrate cells maintained alive on agar blocks on a microscope slide. The parasite is the first strain isolated from a human case in this country, by J. C. Valentine and W. F. Lane. The parasite was shown gaining access to cells by two methods: (A) passively owing to phagocytosis by the cell, and (B) actively by invasion of cells by motile forms.

Reference was made to the fact that there was a great deal to be learned about the methods whereby protozoal parasites, including Plasmodia, Babesia and other intracellular parasites, gain access to infected cells. A joint paper will appear in another place at a later date.

Dr. C. H. Smith, Department of Pathology, Institute of Ophthalmology, London.

Histological Appearances

Toxoplasmosis, if it is as widespread as serological studies would indicate, must be as protean in its manifestations as tuberculosis or syphilis. As with the latter disease, we have both congenital and acquired forms. The congenital infection may manifest itself as an acute encephalitis which may lead either to fœtal death or to a fatal infection in the newborn, or have remote sequelæ such as hydrocephalus and chorio-retinitis. In the adult the disease may be fulminating and simulate typhus fever, or may be less acute and present, for example, as a case of glandular fever or of chorio-retinitis. Finally, if our laboratory studies are correct, a large percentage of persons must be infected without any apparent pathological lesion being produced.

Histology.—If we first consider the lesions produced by this parasite in its more acute infection, the paucity of the histological response is remarkable. Thus in the detailed accounts given by Valentine *et al.* (1953) of the post-mortem appearances in a baby, and by Sexton *et al.* (1953) and Pinkerton and Henderson (1941) in adults, one is impressed by the fact that very little is seen macroscopically, except that there is usually pneumonic consolidation, and there may be a skin eruption. Despite this, parasites may be found in many organs, e.g. heart and muscle.

The only characteristic changes are in the brain in which small yellowish areas of gliosis may be seen. Some neonatal cases show evidence of hydrocephalus but this is more frequently a feature of the cases which survive for months or years after birth. Calcification has been noted infrequently in these neonatal cases.

Microscopically there is very little which is specific in the neurological lesions, there being a cellular reaction which is predominantly of lymphoctyes and plasma cells, while glial proliferation is found around the foci in which the nerve cells are being destroyed. The vessels show perivascular cellular proliferations and frequently necrosis of the surrounding tissue. In fact, in the absence of the isolation of parasite, differentiation from other focal forms of encephalitis would be difficult.

In some cases the neurological lesions may take the form of a microglial nodule which may be scattered anywhere throughout the C.N.S.; such lesions were present in the case originally described by Wolf and Cowen (1937). More recently, similar nodules have been described in other animals, and in chickens they may reach a considerable size simulating gliomata, as indeed they were believed to be until Erichsen and Harboe (1953) showed their toxoplasmic nature.

Turning to the eye, we again find that the histology is not of a highly specific character, and this is not surprising as many of these eyes were originally thought to be tuberculous. It was not until 1952, when Wilder described the presence of bodies morphologically identical with toxoplasma in sections of eyes removed for acquired chorio-retinitis, that the probability of the parasite being a cause of adult chorio-retinitis was recognized. In the cases which Wilder (1952) described, the disease was typically a posterior uveal infection in which necrotic lesions of the retina and choroid appeared. In addition to the severe lesions posteriorly, there may be a diffuse infiltration of the uvea with chronic inflammatory cells.

Duke-Elder *et al.* (1953) described a case. The Figures 1 and 2 also belong to this case. The retina showed a necrotic lesion posteriorly (Fig. 1) on one side of the optic disc, with cellular infiltration and fusion of the retina and choroid and considerable destruction of the pigment epithelium and Bruch's membrane (Fig. 2). These slides show how well localized are the lesions. Chronic inflammatory nodules were also present in the iris and there may be diffuse cellular infiltration of the choroid (Fig. 3).

Following Wilder's report (1952*a* and *b*), Woods and his collaborators (1954) have, in retrospect, diagnosed many of their granulomatous uveitis cases as of toxoplasmic origin. These cases had previously been considered as brucellosis and tuberculosis, and they now consider that 25% of such cases may have a toxoplasmic origin. In the present communication the term "granulomatous" has been deliberately avoided on two grounds; first, it has been condemned by some pathologists (i.e. Willis) who believe the term serves no useful purpose, and secondly because we believe Woods' correlation of "granulomatous pathology" and a parasiticism of the eye is unjustified since many non-living foreign materials can induce a typical granulomatous type of reaction.

Considering for a moment the evidence for these acquired chorio-retinal lesions being regarded as of a toxoplasmic nature, there are three main grounds upon which this can be based:

(1) *Demonstration of the parasites.*—Crescentic bodies similar to known toxoplasma, can be demonstrated in the ocular lesions. These bodies were first seen by Wilder (1952) in the eye lesions, and were also present in the eye of the case described by Duke-Elder and others (1953). The crescentic bodies are morphologically identical with the toxoplasma, although it should be borne in mind that they must be differentiated from the following:

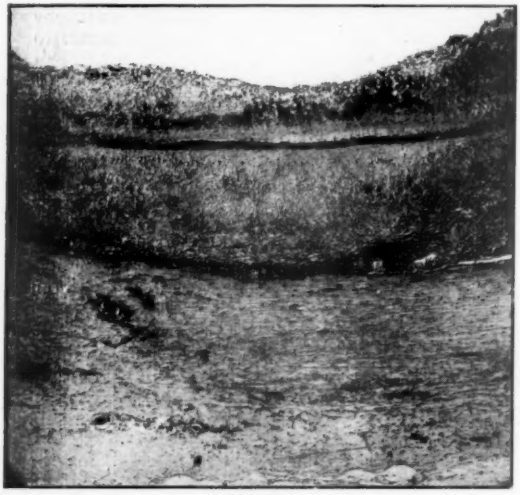

FIG. 2.

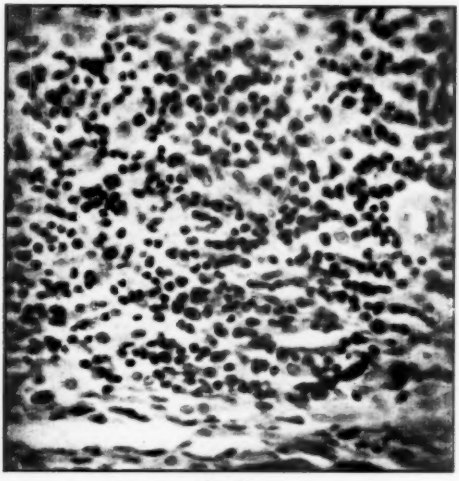

FIG. 3.

FIG. 1.

FIG. 1.—Sagittal section through the globe to show a toxoplasmic lesion at the posterior pole.

FIG. 2.—Low-power view of a localized necrotic focus in the retina and choroid due to toxoplasmosis.

FIG. 3.—High-power view of diffuse cellular infiltration of the choroid in a case of congenital toxoplasmosis.

(i) Cellular debris—this may be very difficult, particularly in sections from eyes embedded in celloidin, which are relatively thick.

(ii) Histoplasma—this organism shows the characteristic staining reaction of yeasts with the leucofuchsin technique.

(iii) Encephalocytozoon
(iv) "P" organism of Frenkel

} Neither of these protozoon parasites has as yet been described in the eye, but both are difficult to differentiate from toxoplasma in the C.N.S. lesions. However, differential stains have been described by Perrin (1943).

Diagnosis of parasites is also made easier if a pseudo-cyst can be demonstrated and it has been suggested that rupture of such a pseudo-cyst may be the means by which a flare-up in these cases occurs—the release of the organism from a cyst either initiating a secondary invasion of the retina or, alternatively, evoking an allergic response.

(2) *Experimental lesions.*—Experimental evidence published by several workers has demonstrated that toxoplasma may give rise to a chorio-retinitis. Hogan (1951) has produced a chorio-retinitis by the injection of material through the carotid artery, showing that it is possible for a blood-spread infection to give a retinal lesion. In this case, however, it was only possible to study acute lesions, as the animals died of an overwhelming systemic infection. Busacca and his colleagues (1952) have succeeded in producing chronic ocular lesions in birds, in which the histological picture is almost identical with that seen in human chorio-retinitis. There was, however, this difference—in the birds which they used numerous pseudo-cysts were found, whereas in human eyes these structures are uncommon. It is of interest that the lesions were in the posterior segment of the eye, and the authors suggest that the disease commences as a pure retinitis and the choroid is only later affected. Ashton (1954), from the histological material he has examined, also believes that the lesions are initially retinal with secondary choroidal involvement. If this is, in fact, the case, it would be in keeping with the known predilection of the organism for nervous tissue and would explain the localization of the disease to the posterior part of the eye, as has been suggested by the higher incidence of positive antibody tests in cases of posterior uveitis.

(3) *Serological studies.*—While it has been conclusively shown by many workers that there is a relationship between toxoplasmosis and chorio-retinitis in children, until recently such a study had not been made upon cases of acquired chorio-retinitis. There are now, either published or in press, a number of reports of such correlations. Thus Duke-Elder's case showed a high toxoplasma antibody, and Hudson (unpublished) has a similar case, whilst Wilder, Jacob and Cook (1953) have recently shown that all the cases in which Wilder demonstrated toxoplasma in eye sections, have a circulating toxoplasma antibody, although this was frequently of a low titre.

There are two more studies which should be mentioned in this connexion; first, that of Woods (1954) at the last American Congress of Ophthalmology to which I have already referred and in which he stated that he believed that up to 25% of uveitis of unknown ætiology might be due to toxoplasmosis. His report, however, is open to criticism of the methods by which his data were analysed and of the arbitrary way in which positive serological titres were considered significant.

The other study I would mention is our own in which over 100 cases of active anterior uveitis have been shown to have the same toxoplasma antibodies as would be present in healthy persons of similar age groups—again suggesting that the toxoplasma lesions are posterior in origin.

In relating serum antibodies to histological lesions in the eye, however, two points should be noted. The first is that titres do not show a constant relationship; e.g. in two cases described by Wilder, cases in which eyes had been removed at approximately the same interval before serological tests were performed, one had a titre of over 1,000 and the other of only 4. This might or might not be due to the intensity and duration of the stimulus for antibody production or because the titres are not related to the eye lesion.

The second point is that there may be a correlation between toxoplasma antibody and the Middlebrook-Dubos Test. This has already been reported from Germany, and not infrequently in our cases both tests are positive at one and the same time.

The ideal method for the diagnosis of any condition is, of course, the isolation of the parasite from the lesions, but the chief difficulty in ophthalmology is to obtain material from the living eye—our most readily obtainable intra-ocular fluid being aqueous.[1] Up to the present time no toxoplasma has been reported in this fluid, although Amsler and Verrey have carried out some thousands of such aspirations, and many other workers have wide experience of the technique. Cultural studies on the aqueous by Busacca *et al.* (1952) in France, Murray (1953) in Canada and ourselves in this country, would almost certainly have revealed the presence of the parasite if it were present in appreciable numbers in the anterior parts of the uveal tract. That the parasites are not free in the aqueous is not surprising if, as I have already suggested, the lesions are essentially posterior.

[1] Since this paper was read Toxoplasma have been isolated from the eye (Jacobs, L., Fair, J. R., and Bickerton, J. H., 1954, *Arch. Ophthal., Chicago*, **51**, 287).

Summary.—Our experience has been that toxoplasmic chorio-retinitis is a definite entity, but its histology is not sufficiently characteristic to enable us to diagnose the condition without the demonstration of the parasite in the lesion. Furthermore, considerable care must be exercised before asserting that any particular body appearing in a section is truly a toxoplasma. In fact it is probably impossible to make a diagnosis of toxoplasmosis on any single feature either clinical, histological or serological. While serological studies may help us to decide if a case is one of toxoplasmosis, I believe that a single observation of a titre can seldom be considered diagnostic, and the problem of serological diagnosis is similar to that of influenza or other widespread infections in which a changing titre is the only acceptable serological test.

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Mr. J. R. Hudson: *Clinical Aspects of Toxoplasmosis*

Since Vail's paper (1943), in which the clinical details of toxoplasmosis were introduced to the literature, and more particularly since Ridley's paper (1949), a number of reports of cases have appeared in ophthalmic, medical and pathological journals. The natural history of the disease is therefore well known, and my remarks will be largely confined to the experience gained by the examination of a series of cases in the Clinical Research Department at the Institute of Ophthalmology. This limitation excludes the acute systemic disease in infants; details of such a case are given in a recent paper (Ballantyne *et al.*, 1953). No case of this type is likely to be seen at an eye hospital, and as the outcome in severe cases of pre-natal infection is often fatal, as it was in the case just mentioned, the diagnosis can be confirmed pathologically by histological methods and by transmission of the disease to laboratory animals. The pathological findings include a granulomatous encephalomyelitis and a localized choroido-retinitis. Table I indicates the diverse nature of the clinical signs. The less severe pre-natal cases survive for a longer period, and the disease may present with any of these clinical features. The ocular findings reported are almost as variable as the manifestations of the systemic disease, as will readily be seen from Table II.

Table I.—Ocular Manifestations

Nystagmus	Vitreous opacities and organization
Convergent or divergent squint	Choroido-retinitis
Microphthalmos	Optic atrophy due to papillœdema or to choroido-retinitis
Iridocyclitis with synechiæ	Papillœdema due to hydrocephalus
Secondary cataract (following uveitis)	

Table II

Signs Secondary to Encephalomyelitis	General Signs
Convulsions	Feeding difficulties
Muscular spasticity and opisthotonos	Fever
Muscular twitching or paralysis	Jaundice
Exaggerated reflexes	Enlarged liver and spleen
Respiratory difficulty with cyanosis	
Vomiting and diarrhœa	
Hydrocephalus, cerebral calcification, microcephalus	
C.S.F. changes—xanthochromia, pleocytosis, elevated protein content.	

Incidence of toxoplasmosis as a cause of ocular disease.—Choroiditis ranks with anterior uveitis as one of the most investigated and least diagnosed conditions in ocular pathology, and I often wonder whether a positive finding during the course of investigating a case of iritis is not just a coincidence—whether in a control series of patients with normal eyes an equally high percentage

of positive findings might not result. Toxoplasmosis should only be diagnosed when the laboratory investigations and clinical evidence all point in the same direction. I am loth to make the diagnosis, certainly in the younger age groups, unless the clinical findings on ophthalmological and X-ray examination are supported by significant serological titres.

The common presenting features in patients who have had a toxoplasma infection, and the confirmatory findings.—In children under 10 years of age, the infection is most likely to have been pre-natal, and the usual clinical appearance is a healed choroido-retinitis at the posterior pole, involving either the macular area or its vicinity. The actual fundus appearances are illustrated, together with the skull X-rays of a few characteristic cases in the case reports (Figs. 1–6). Of the serological tests, the cytoplasm modifying dye test is the most reliable, and although very high titres have been reported in American papers, in this country relatively low titres are clinically significant. Table III shows the titres regarded as significant in the various age groups. The third important confirmatory finding is that of intracranial calcification, or evidence of internal hydrocephalus or microcephalus, visible on radiographic examination.

TABLE III.—TITRES REGARDED AS SIGNIFICANT IN THE VARIOUS AGE GROUPS

Years	Titre
Under 10	1 : 16 or over
10 to 19	1 : 32 or over
Over 20	1 : 64

In the present investigation, of 19 cases of choroido-retinitis under the age of 10 years, 9 gave a negative dye test, of which none had evidence of intracranial calcification. Of the 10 cases with a positive dye test, the titre was under 1 : 10 in 2 cases, and over 1 : 16 in 8. Of these 6 had intracranial calcification. The highest titre was 1 : 1,000 (Table IV). Although this is a short series, roughly one-quarter of the cases referred were confirmed cases of toxoplasmosis. The observation of healed choroido-retinitis in a child should, therefore, raise the possibility of a congenital toxoplasma infection with investigation by serological tests and radiography.

In the next age group, from 10 to 19, of 20 cases, 7 had a negative dye test, and of the remaining 13, 7 had a positive dye test of significant titre. None of these showed calcification. Of the other 6, one had intracranial calcification (Table V). In this age group it seems less likely that a case of choroido-retinitis would be due to toxoplasmosis, but here the presence of calcification in a case with a low serum titre and choroido-retinitis raises the possibility that toxoplasmosis may be the diagnosis, although the serum titre has fallen to an apparently insignificant level.

In the third age group, 20 years of age and over, of 38 cases, 17 had a negative dye test, and of the remaining 21, only 2 had a titre of over 1 : 64. Of the 19 with a titre of under 1 : 64, 1 with a titre of 1 : 36 showed evidence of calcification. One case, in which the titre rose to 1 : 800 has been reported recently (Hudson, 1954), as a probable case of adult toxoplasmosis. In this case one would not expect to find intracranial calcification (Table VI). Here, again, the one case with intracranial calcification has a cytoplasm modifying dye test not significant by our standards, but surely this is also a case of toxoplasmosis.

TABLE IV.—SUMMARY OF 19 CASES OF CHOROIDO-RETINITIS UNDER THE AGE OF 10 YEARS

Titre		Calcif. present
Negative	9	–
Up to 1 : 10	2	–
1 : 16–1 : 31	2	2
1 : 32–1 : 63	2	1
1 : 64–1 : 80	1	1
1 : 81–1 : 160	2	1
1 : 1,000	1	1

TABLE V.—SUMMARY OF 20 CASES OF CHOROIDO-RETINITIS IN AGE GROUP 10 TO 19 YEARS

Titre		Calcif. present
Negative	7	–
Positive (no titre)	1	–
Up to 1 : 10	3	1 (1 : 5)
1 : 11–1 : 15	1	–
1 : 16–1 : 31	1	–
1 : 32–1 : 63	4	–
1 : 64–1 : 80	1	–
1 : 81–1 : 160	1	–
1 : 640	1	–

TABLE VI.—SUMMARY OF 38 CASES OF CHOROIDO-RETINITIS IN AGE GROUP 20 YEARS AND OVER

Titre		Calcif. present
Negative	17	–
Up to 1 : 5	3	–
1 : 5–1 : 10	6	–
1 : 16–1 : 31	3	–
1 : 32–1 : 63	7	1(1 : 36)
1 : 64–1 : 80	1	–
1 : 8,000	1	–

The results suggest that in young children the diagnosis of toxoplasmosis must be seriously considered, whereas in the higher age groups other causes are likely to be responsible for a higher percentage of cases of choroido-retinitis.

The problem of active choroido-retinitis in the adult is quite separate from the consideration of the cause in those cases where the healed condition may be found in routine examination. What are the clinical findings in these cases? Dr. Smith has mentioned the relatively small number of cases of anterior uveitis referred to the Uveitis Clinic in which there was even a suggestion that the toxoplasma might be the infecting agent, and as I have been confining my attention to the choroido-

retinal manifestations, I will not pursue the clinical aspects of toxoplasma infection as a cause of iridocyclitis.

Of the 58 cases over the age of 10 years, 34 had a positive serum titre—including those in whom the titre level was not considered to be significant—and, of these, 13 had active choroido-retinitis. The clinical appearances on ocular examination varied from that of a localized solitary focus or the more characteristic bilateral condition, with relatively large areas of active choroido-retinitis, to a generalized uveitis with active K.P. and vitreous haze. Intracranial calcification was not a feature.

There is no typical or characteristic X-ray appearance of intracranial calcification due to toxoplasmosis. As will be seen from the X-rays, each case is different, and the literature includes descriptions of many of these. There may be diffuse small areas scattered through the outer layers of the cortex, or a few isolated areas deeper in the brain substance, sometimes appearing in the paraventricular regions, and in other cases there are curvilinear streaks in the region of the basal ganglia. Nor, of course, is intracranial calcification confined to cases of toxoplasmosis. It may also occur in a number of other conditions, and Sutton (1951) has described the different types of intracranial calcification and the differential diagnosis in detail.

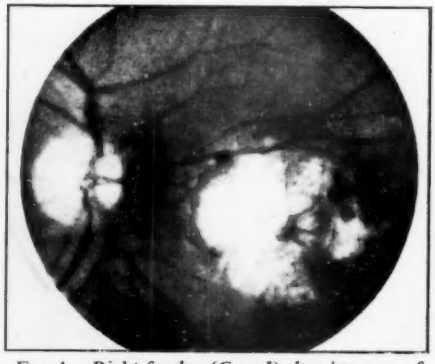
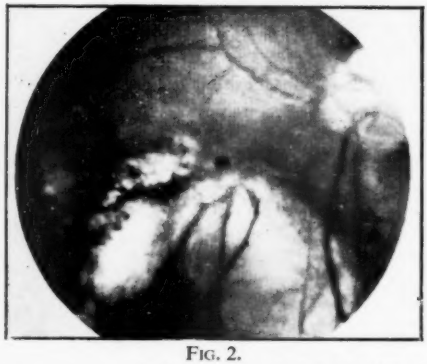


FIG. 1.—Right fundus (*Case 1*) showing area of choroido-retinitis nasal to disc.

FIG. 4.—Skull X-ray (*Case 1*) showing areas of calcification in region of basal ganglia.



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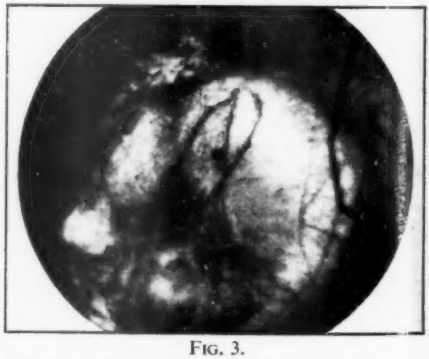

FIG. 3.

FIGS. 2 and 3.—Left fundus (*Case 1*) showing lesion below and nasal to disc.

The following are a few illustrative case histories:

Case 1.—Boy of 20, complaining of poor distant vision and headaches. The family and environmental history were not relevant, and the patient's own history was uneventful until the age of 10 years, when he had jaundice, with hepatic and splenic enlargement, and was subsequently said to have developed a "spot at the back of the eye". At the age of 13 years he had four fits at close intervals, but has had none since. He later served in the Armed Forces, from which he was invalided on account of "blackouts". The fundus appearances in each eye are shown in Figs. 1–3, the scar in the right eye giving clinically the impression of a second optic disc, and Fig. 4 shows the X-ray findings of areas of calcification in region of basal ganglia and in the cerebral cortex. The cytoplasm modifying dye test gave a positive titre of 1 : 36, and the complement-fixation test a titre of 1 : 8. The possibility here is that this is a juvenile type of toxoplasmosis.

Case II.—Boy of 18, with no relevant family or personal history, had a convergent squint, nystagmus, and a corrected visual acuity of 6/60 in the right eye and counting fingers in the left. There were areas of healed choroido-retinitis in both eyes, and the skull X-ray shows paraventricular calcification (Fig. 5).

Case III.—A twin boy of 8½, has a left convergent squint, a normal right fundus, patches of choroido-retinal degeneration in the left fundus, paralysis of his palate, and weakness of the left hand. His dye test is positive to a titre of 1 : 32, complement-fixation test 1 : 4. His twin brother is a normal healthy child, with normal fundi, a negative dye test, and "doubtful" complement-fixation test (1 : 8). It is very interesting to find twins, one of whom appears to be a case of toxoplasmosis, and the second of whom seems to have escaped infection. So far no further investigations have been done to establish whether these are identical twins—the difference in their appearance could be accounted for by the effect of the infection on one of them. Until recently it has been generally agreed that it is rare for more than one member of a family to be affected, but Campbell at the Royal Society of Medicine (1953) produced family histories which strongly suggested that more than one member of the same generation was involved, but not necessarily congenitally. Fig. 6 shows the skull X-ray.

Case IV.—A boy of 15, had bilateral choroido-retinal degeneration in the perimacular areas of both eyes, a cytoplasm modifying dye test titre of 1 : 64 and a complement-fixation test of 1 : 40. He had no cerebral calcification.

Case V.—A male patient, aged 36, who first attended Moorfields in 1951, complaining of recent deterioration of the vision of his right eye. On examination he was found to have a small patch of active choroiditis near

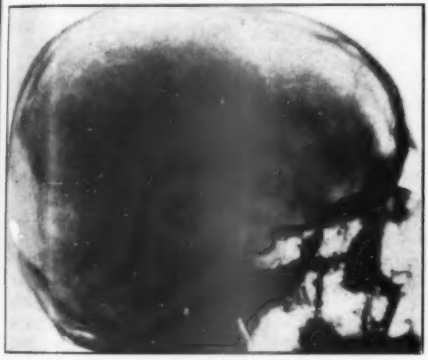

FIG. 5.

FIG. 6.

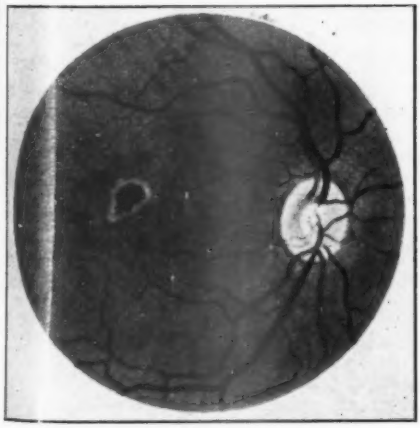

FIG. 7.

FIG. 5.—Skull X-ray (*Case II*) showing paraventricular calcification.

FIG. 6.—Skull X-ray (*Case III*) showing diffuse calcification in cerebral cortex.

FIG. 7.—Right fundus (*Case V*) showing healed choroido-retinitis near right macula. (Reproduced from *Brit. J. Ophthal.* (1954) **38,** 180, by permission.)

the macula. This subsided gradually, leaving a small healed choroido-retinal lesion shown in Fig. 7. The left fundus is normal. This patient has a normal skull X-ray, and the dye test when first done in 1951 was positive to a titre of 1 : 30, complement-fixation test 1 : 20. He received treatment with systemic

cortisone both intramuscularly and in tablet form. The visual acuity when first seen was 6/9 and fell to 6/24 during the first month. It has subsequently improved to 6/9, and the present appearance of the lesion is unchanged. The W.R. was negative. The mother's blood was examined as a routine, and gave a dye test of 1 : 4, and a negative complement-fixation test. The rise in titre in this case appears to be significant, and it is now being repeated at monthly intervals (Hudson, 1954).

With regard to treatment, many drugs have been tried experimentally and a few clinically, but have been proved ineffective in human beings. The sulpha drugs, of value in some instances in experimental infection, have been unsuccessful clinically. Penicillin, streptomycin, and aureomycin have failed to control experimental infection. Professor Beattie (1953), working with D.D.S. (diamino-diphenyl-sulphone), found it had a definite effect in preventing the death of mice and in reducing the eye lesions of rabbits. Results were still better in rabbits when cortisone was given as well.

This investigation has been made possible through the help of the members of the staff at both the Moorfields and Westminster branches of the Hospital, from whose clinics nearly all the cases were referred, and whom I should like to thank for their interest. I should also like to acknowledge the very considerable assistance provided by the Pathological and Medical Illustration Departments at the Institute and the X-ray department at Moorfields.

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Mr. Gayer Morgan asked how the human subject was infected. Was it necessary to eat infected food? Did one get it on the hands by contact with animals or must one eat the flesh of an infected animal which had not been properly cooked?

Dr. I. A. B. Cathie said that as a result of considerable serological work on this condition he thought that the dye test titres accepted as evidence of toxoplasmosis by the previous speakers were too low. Dye test titres higher than those mentioned were so frequently seen in normal adults who had no evidence of toxoplasmosis at all that he had come to rely more and more on the complement-fixation test, which should be positive at a titre of 1 : 8 or more for the diagnosis of toxoplasmosis to be considered. He felt further that sufficient distinction had not been drawn between active and burned out, or congenital toxoplasmosis, as in the former both dye and complement-fixation tests would be positive, whereas in the latter although all the stigmata of toxoplasmosis might remain the complement-fixation test had frequently become negative. He had looked through his figures, and found that in sera from some 300 cases of choroido-retinitis where clinical details were supplied, from different parts of the country, 60, in round figures, gave results thought to be diagnostic of toxoplasmosis.

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Mr. Hudson, in reply to Mr. Gayer Morgan, said that the mode of infection was not known, but transmission from mother to infant was presumably trans-placental.

JOINT MEETING No. 4

Section of Neurology with Section of Pædiatrics

Chairman—REDVERS IRONSIDE, F.R.C.P.
(Vice-President of the Section of Neurology)

[*December* 3, 1953]

DISCUSSION ON THE NEURO-OPHTHALMOLOGICAL ASPECTS OF FAILURE OF VISION IN CHILDREN

Mr. J. H. Doggart:

Within living memory the opinion of an ophthalmolcgist about a patient's optic discs could settle the question whether that patient's skull was to be opened; and indeed I happened, some twenty years ago, to examine a middle-aged woman who had as a girl undergone craniotomy by Horsley, mainly on the score of her angry-looking discs. These discs were deep crimson, and had no recognizable margins, *and* they jutted forward slightly but appreciably beyond the neighbouring part of each fundus. The patient's headaches were relieved, after she had recovered from the operation, by glasses to correct her compound hypermetropic astigmatism.

Now that neurological clinics and cranio-surgical units have at their disposal the pneumogram, the angiogram, the electro-encephalogram and other modern devices, ophthalmologists take less share in diagnosing a doubtful case of central nervous disease. As an ophthalmologist I can but admire anyone who can thread his way through this labyrinthine central nervous system, but not many neurologists rest content with that achievement. Some of them launch out into metaphysics. Others reconstruct their forefathers' lives in a neurotropic mould. Yet another keeps on castigating loose thought and the inaccurate use of words; but perhaps the hallmark of a neurologist is intense concentration upon any problem to which he is committed. That is why Henry Head was cut short when he rushed up to Hughlings Jackson one day, eager to dilate upon his latest clinical discovery. "Don't bother me now, Head, I'm making some observations on my own migraine."

Migraine, by the way, is commoner among children than many people suppose. Hunt (1933) pointed out twenty years ago that bilious migraine in children is often diagnosed only in retrospect, because children are so seldom analytical in their description of symptoms. If the attacks persist into adult life, as they often do, then the meaning of those early symptoms can be grasped. Krupp and Friedman (1953) have just published a study of 50 children suffering from this complaint, and clearly migraine has to be borne in mind as a possible source of visual disturbance in early life. It is interesting to note that the original case of Fröhlich's (1901) syndrome was diagnosed as migraine because at first no abnormality of the patient's fundi was detected.

SYMPTOMS OF VISUAL FAILURE

When visual failure in a child is of neurological significance, there are usually symptoms to suggest that the trouble is not entirely ocular. Gordon Holmes (1946) stressed the importance not only of symptoms originally volunteered by the patient, but also of those which can be elicited by judicious enquiry, always with due avoidance of leading questions.

In dealing with small children we depend mainly upon the testimony of adults, but let us also hear the child's own version. From the age of 4 years, and sometimes even earlier, many children are capable of lucid description, especially if their parents are not in the room. We should take a careful note of past illnesses and injuries, paying special attention to those which may implicate the nervous system and visual apparatus. Previous ear trouble can be relevant. Personality changes, rapid alteration in weight, giddiness, fainting attacks, double vision, sudden variations in sight, headache and vomiting may be significant. Family history will often supply a clue in the various types of hereditary ataxia.

Exposure to poisons should be considered in certain cases, as, for instance, the danger of lead-poisoning from lollipops and ice-cream. Not long ago there was a boy in Great Ormond Street suffering from severe lead encephalopathy because he had been gnawing toy soldiers. Ford (1946) assembled 40 such cases, and he quoted similar reports by Japanese authors. Swelling and subsequent atrophy of the optic discs have been repeatedly observed in lead poisoning.

SIGNS

Although neuro-ophthalmic disease is *usually* foreshadowed by symptoms, examination of the eyes must, nevertheless, be vigilant, because from time to time we shall find a pair of swollen discs in a child who still sees perfectly, and is not complaining of symptoms.

Non-ophthalmoscopic manifestations.—The shape of the face and skull will often be suggestive, because so many skeletal defects are linked with neuro-ophthalmic disease, facial weakness is also suggestive. Nystagmus may be ocular, i.e. pendular, in which the to-and-fro elements are of equal speed, or labyrinthine, which can be analysed into rapid and slow components. Proptosis of one or both eyes may put us on the track, and the ocular motility is important.

Movement of either eye may be limited or excessive in one or more directions, but we should also note abnormal obliquity. If, for instance, a patient's right eye rises when he looks to the left, we speak of a right upshoot, which indicates overaction of the right inferior oblique muscle; and that in its turn usually means paresis either of the left superior rectus, or of the right superior oblique. In the vertically-acting extraocular muscle it is not always recognized that the superior and inferior rectus muscles, although they happen also to be adductors, exert their maximum *vertical* effect when the eye is abducted. On the other hand the inferior and superior oblique muscles are at their best as an elevator and a depressor respectively, when the eye is adducted, although admittedly these oblique muscles are both abductors if we are considering their isolated actions.

There may be a lack of power to converge both eyes upon a near object, and while we note the pupils and their response to stimuli, we should remember that many abnormal pupils can be explained by the state of the eye itself, as a traumatic mydriasis, miosis from posterior synechiæ, and anisocoria due to asymmetrical development of the iris musculature.

I must omit those interesting opacities in the ocular media which may have a neurological bearing. When we come to look at the fundus, attention will centre chiefly upon the optic discs, but other signs need not be neglected. In Batten's disease, for example, we may find pigmentary changes in the periphery of each retina, together with macular degeneration, as well as partial consecutive optic atrophy. Syphilis can produce multiple patches of peripheral choroido-retinitis, or may attack the macula, and occasionally leads to neuro-retinitis. The large plaques of choroido-retinal degeneration created by toxoplasmosis are now well known, and various bizarre lesions may be evolved in the phakomatoses.

The optic disc itself is often misinterpreted. In the first place many people do not realize the wide range of colour displayed by normal discs, and so they tend to diagnose optic atrophy without justification. Secondly it is too often assumed that a disc with indistinct margins is necessarily swollen. A third fallacious belief is that, if an observer with relaxed accommodation can appreciate details on the disc-surface through a strong convex lens in his sight-hole, he must be dealing with a swollen disc. A fourth source of error is the variability within normal limits of the calibre and disposition of the vessels. Incidentally we often find wisps of embryonic connective tissue filling the physiological cup and even extending beyond. These harmless vestiges have been mistaken for the signs of secondary optic atrophy.

Blurring of the disc margin is common in compound hypermetropic astigmatism, but it may occur even in emmetropes. Moreover hypermetropia reduces the dimensions of an eye, so that the nerve-bundles jostling through the lamina cribrosa may produce a slight bulge not constituting genuine disc-œdema. Slight salience of the disc should not be interpreted as pathological unless we find corroborative signs. In measuring the swelling, the actual strength of the final lens in the sight-hole of the ophthalmoscope can be ignored. What matters is the *relative* strength of that lens compared with the strength of the lens which proves best for the adjacent part of the fundus. Suppose that the observer with relaxed accommodation sees details on the surface of the disc through a + 5·0 dioptre lens. If adjacent details are also clear with a + 5·0 lens, then there is no swelling of the disc. If, however, adjacent details require a + 1·0 lens, we can take it that there are about 4·0 dioptres of swelling.

For every case of true disc-œdema, I must have been shown at least four allegedly suffering children in whom there was no visible swelling, and it seems clear that many people diagnose or suspect disc-œdema simply because the consequences of missing it may be so grievous. In reality there need seldom be any serious doubt about the presence of œdema, provided that the observer appreciates those sources of fallacy which I have mentioned. Furthermore a true disc-œdema is usually accompanied by corroborative signs, especially turgidity of the retinal veins, and flecks of hæmorrhage on and near the disc. One noteworthy feature of disc-œdema in children is its swift development. More than once I have seen several dioptres of swelling in a child whose discs were free from œdema less than forty-eight hours previously. One important consequence of this rapid emergence is that the swelling soon seeps over to the macula, unless the intracranial pressure can immediately be lessened. This macular œdema is followed by central choroido-retinal atrophy and pigmentary degeneration.

Subjective Testing

The visual acuity of children who do not know their letters can often be ascertained by means of the "E" test. In selected cases orthoptic investigation of the binocular function helps, and the Hess screen test performed at intervals is useful as a comparative record in cases of muscular paresis. The confrontation field test, whenever it is feasible, should be done separately for each of the four quadrants of both fields. Perimetry may locate a lesion involving the visual pathways, but many of the children suffering from neuro-opththalmic disorder, even if they are old enough for chartin of their visual fields, will be too ill to concentrate. The same limitation applies to testing on the Bjerrum screen. Enlargement of the blind-spot is commonly cited as conclusive evidence of disc-œdema, but it must be remembered that there is some normal variation in the size of the blind-spot; and that, as a rule, true swelling is unequivocally evident by ophthalmoscopy, if that examination be performed by an experienced observer.

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Mr. G. I. Scott (Edinburgh): I propose to confine my remarks to two subjects: First, one of the demyelinating diseases, *Neuromyelitis optica*, with particular reference to its occurrence in children. Second, *Retrolental fibroplasia*, or the retinopathy of prematurity, and the possible significance of the fact that, not so very rarely, a number of the babies who suffer from this defect later develop spastic diplegia.

(1) NEUROMYELITIS OPTICA

In a follow-up of 10 cases of neuromyelitis optica, seen in Edinburgh during the period 1937–1949 (Scott, 1952), two of the cases were typical of the disease in that they developed bilateral optic neuritis, preceded or followed by paraplegia as well as other obvious signs of myelitis. Both were adults.

I also have records of 2 other cases seen in 1938 and in 1939, but as I saw neither at the commencement of the disease, and have only been able to follow up one, I excluded them from my survey. In both, however, the optic neuritis preceded the myelitis, and both made a complete recovery from the optic neuritis although they were left with residual effects from the myelitis.

In this type of case, it is generally recognized that the mortality is in the region of 50%, some dying in a matter of weeks, others surviving for a number of years, and some making a partial or even a complete recovery.

Walsh (1935) has drawn attention to cases in which there is binocular loss of vision not followed by paraplegia, and has expressed the view that these cases represent an abortive form of neuromyelitis optica, since symptoms referable to the spinal cord are often minimal.

I am sure that we should recognize that cases of neuromyelitis optica do, in fact, fall into two main groups, the first, the classical type of case, to which I have already referred, and the second and, I think, much larger group, in which there is bilateral optic neuritis, but in which signs of myelitis, although quite definite, are much less obvious and in which the motor pathways are hardly affected.

Of my remaining 8 cases, which were first seen during the period 1937–1949, one with onset of the disease in 1939 died in the same year, but the remaining 7 still survive and have now been followed up for periods varying from eleven to sixteen years.

This latter group includes 4 children.

Before referring to the children, I would like to describe the signs and symptoms occurring in one of my patients, a boy of 16, since he demonstrates very clearly the features which adults or adolescents in this group seem to present. In children, there is, of course, often great difficulty in getting satisfactory responses to tests of sensation and I find difficulty in distinguishing such cases, if they are at all atypical, from those of acute disseminated encephalomyelitis.

Case I.—J. I., male, aged 16. First examined May 1940.

History.—Transient attacks of *blurring of vision left eye*, lasting a few minutes each time, for one week: six days later vision in both eyes noticed to be dim on waking, and by next morning could only see hand movements. At the same time he had a temperature, and complained that he had sore knees when walking.

Examination.—V.A.—Hypermetropia in both eyes.

2.5.40: Increased tendon reflexes all four extremities. No pathological sensory findings. No weakness in limbs. R.V. J.4. L.V. J.10. 24.6.40: R.V. 6/6 and J.1. L.V. 6/6 and J.1. 26.6.40: Moderate rise of temperature. Stiffness of neck. Tingling paræsthesia, on both sides, on anterior aspect of thighs. 29.6.40: *Complete retention of urine. Marked tingling paræsthesia up to Th.*10. Abdominal reflexes absent. *Marked bilateral Babinski sign.* No motor weakness. Neck rigidity and ? Kernig sign. During the following week the level of sensory disturbance ascended to Th.4. 15.7.40: Sensory level down to Th.10.

C.S.F.—Cells 3 per c.mm. Total protein 30 mg. per 100 ml. Colloidal gold curve negative. W.R. negative. 30.7.40: Plantar responses now flexor. 3.8.40: Suprapubic wound (cystostomy) dry. No weakness. No sensory disturbance. Reflexes normal. 31.8.40: Discharged from hospital.

Examined 20.10.46 at age of 22.

History.—Sudden recurrence of loss of vision in left eye, two days ago.

Examination.—R.V. 6/6 J.1. L.V. ? perception of light. Discs somewhat pale. Well defined. 23.10.46.; Loss of vision *right eye*. R.V., now ? perception of light. L.V., sees hand-movements.

C.S.F.—15 cells per c.mm. Protein 40 mg. per 100 ml. Colloidal gold negative. 12.11.46: R.V. 1/60. L.V. 1/60. 10.12.46: R.V. 6/12. L.V. 6/12. Both discs very pale. 7.1.47: R.V. 6/6 (−1). L.V. 6/6 (−2). Reads Jaeger 1, scotomatously.

Follow-up, 1953.—R.V. 6/6 partly and Jaeger 1. L.V. 6/6 partly and Jaeger 1.

Minute paracentral scotoma, in each field, to 3/2,000 red test object.

Marked pallor of optic discs, more marked on left side.

Summary.—(1) Bilateral optic neuritis, April 1940. (2) Acute myelitis, May to July 1940. Recovery from optic neuritis and myelitis. (3) Recurrence bilateral optic neuritis, October 1946, with practically complete recovery.

With regard to the 4 children in my series of cases, one of them, seen in 1939, typifies the picture as I have seen it.

Case II.—M. McS., female, aged 6. First examined 16.3.39.

History.—Four weeks ago—frontal headache which disappeared a few days ago. Three days ago—things suddenly went black: child groped about.

Examination.—Most intelligent and co-operative. *Does not admit perception of light in either eye.* Pupils widely dilated: no reaction to light. Considerable swelling of optic discs. All tendon reflexes normal in upper extremities. Knee-jerks poor, but good on reinforcement. Ankle-jerks poor. Abdominal reflexes brisk.

Sensory findings.—Very consistent in responses.

Pain and cold.—Depressed in both lower extremities. (Upper level for pain is the umbilicus, on both sides.)

C.S.F.—Pressure 150 mm. Protein 35 mg. per 100 ml. Cells 18 per c.mm: Lymphocytes. Wassermann negative. 17.3.39.—No incontinence. No paresis. No ataxia. 25.3.39: *Bilateral extensor plantar response.* 18.4.39: Sensory findings now normal: knee and ankle jerks normal. 25.9.41: V.A. 6/9 and Jaeger 1 (with difficulty) in each eye. (Vision recovered very rapidly May–July 1939.) 13.5.51: R.V. 6/6 (−2) J.1. L.V. 6/6 partly: J.1. Slight pallor of both optic discs. Minute paracentral scotoma to 3/2,000 red, each eye.

Summary.—(1) Bilateral optic neuritis 1939. (2) Myelitis 1939. (3) Recovery: no relapse during fourteen-year period of follow-up.

With regard to the age of onset of the disease, I have selected 50 cases from the literature and these, together with my own 10 cases, show an age distribution quite different from that which one finds in disseminated sclerosis.

Brain (1934) referred to 12 cases of bilateral optic neuritis, which he had seen, without known cause and without any other abnormality developing at the time or subsequently, and he compared the age distribution with that of 26 cases of acute unilateral optic neuritis.

He emphasized that the acute bilateral form fails to exhibit any significant selective age-incidence during the first five decades, in contrast with acute, usually retrobulbar, neuritis which shows a conspicuous peak between the ages of 20 and 40.

Whether or not such cases of severe bilateral optic neuritis represent an even more abortive manifestation of the disease one cannot say, but the comparable age distribution is of interest.

From the point of view of prognosis, the question of the mode of onset is, I think, of some significance. In this connexion, I have been impressed, not only in this series of cases, but also in others which I have seen at one time or another, by the fact that cases which commence with optic neuritis, without preceding signs of involvement of the cord, seem to have a rather better prognosis than do those which develop myelitis as the first major incident, and I am certain that those cases which do not show any clinical involvement of the motor pathways in the first phase of the disease are much more likely to survive than those which develop paraplegia at this stage.

In my own series of cases, the myelitis was first in 1 case, but in the remaining 9 cases the visual loss was the first "major incident". In some cases there may, however, be a history of tingling in one or other hand, or of weakness in an arm, some months before the onset of the optic neuritis, or the optic neuritis may be preceded by a vague history of a tired feeling in the legs.

Pain, often quite severe, either in the eyes or above them, is I think, common at the onset of the disease.

There seems to be no relation between the severity of the optic neuritis and that of the myelitis. 6 of the 12 cases to which I have referred showed only relatively mild signs of myelitis, and yet, in all, the optic neuritis was of a very acute type.

(2) "Retrolental Fibroplasia" or the Retinopathy of Prematurity

In March 1952, we began, in Edinburgh, an examination of all premature infants born in the city. In order to make the task an easier one, and to ensure, as far as possible, that we would be able to follow-up the future development of such infants, we limited our enquiry to premature babies weighing 4 lb. or less at birth, and whose parents were resident in Edinburgh.

We also recalled for examination all babies, satisfying the above criteria, who had been born in Edinburgh during the years 1948–1952, since the first recorded case of the condition, in Edinburgh, occurred in 1948.

This investigation was carried out in conjunction with Dr. J. B. Kerr.

During this five-year period, 1,257 premature babies, of a birth weight of 5½ lb. or less, were born in Edinburgh. Of this number, 240 had a birth weight of 4 lb. or less, and 23 developed what I would like to call "retinopathy of prematurity" or, as it is more generally described, "retrolental fibroplasia" (Fig. 1).

Although we have not yet fully analysed our findings, there are one or two points of interest.

In this series of 1,257 premature babies, we had 11 babies who later developed true spastic diplegia and, of these 11, 10 were in the group of 240 with a birth weight of 4 lb. or less.

Five of these 10 babies had also developed retrolental fibroplasia.

The numbers are, of course, small but the apparent association of these two conditions (Fig. 2), the retinopathy of prematurity and the subsequent development of spastic diplegia is not, I think, without significance when one considers the ætiological factors which might be involved.

Ashton and co-workers (1953) thought it essential, in view of the controversy regarding the role played by oxygen in the ætiology of retrolental fibroplasia, to investigate experimentally the influence of varying concentrations of oxygen upon the immature retina. For this purpose, the kitten was selected in view of the fact that the retinal vessels of the cat do not reach the retinal periphery until about three weeks after birth, and, during the ensuing three weeks, was considered as comparable to the premature baby.

The main conclusions of these preliminary experiments were that high concentrations of oxygen almost obliterated the ingrowing vessels of the developing retina of the kitten. In addition, however, when the animals were returned to air, such vessels as remained patent refilled with blood. The resulting development, however, was grossly abnormal, in that an irregular cobweb of vessels developed at the periphery of the reopened network, following which new vessels later grew into the vitreous, to be followed by retinal detachment.

FIG. 1.—Baby with advanced degree of retrolental fibroplasia.

FIG. 2.—G. B. Retrolental fibroplasia; mental defect and severe diplegia. Showing early rigidity, emerging from the dystonic phase.

One great difficulty in accepting the view that intensive oxygen therapy is the basic cause of the retinopathy of prematurity is the fact that cases have been recorded (Bembridge *et al.*, 1952) in babies who have never had any oxygen therapy at all. We have had one such case in Edinburgh.

I think that it is almost certainly true that retinal vasoconstriction resulting from exposure to oxygen is an important factor in regard to the degree to which the retrolental fibroplasia develops, but I doubt if it is the oxygen which inflicts the basic injury.

In this connexion, the fact that such a large proportion of our Edinburgh cases later developed spastic diplegia is not without interest.

Krause (1946) has pointed out the frequent association of cerebral defects and ocular disease, and has put forward the view that retrolental fibroplasia is only part of a wider failure in the development of the anterior part of the central nervous system.

Szewczyk (1952) considered retrolental fibroplasia as being a terminal stage of an "anoxic retinopathy", induced by retinal oxygen deficiency during a period of life when vascularization of the retina was taking place.

Ingalls (1948) discussing "congenital encephalo-ophthalmic dysplasia", considered that this term covered a common process which might manifest itself in three ways:

(i) by the appearance of structural or dissociated malformation of the cerebrum; (ii) by the

appearance of simple or multiple hæmangiomas of the skin; or (iii) by variable ocular abnormalities such as retrolental fibroplasia.

Ingalls put forward the view that these conditions might arise singly or together, depending upon the stage of development at which toxæmia occurred. In this way, he explained the periodic occurrence together of three apparently unrelated conditions, retrolental fibroplasia, cerebral palsy (with or without mental retardation) and skin hæmangiomas.

It is also of interest to note that Bjelkhagen (1952) in a review of 38 cases of retrolental fibroplasia in Sweden, found that 14 were mentally retarded, in 13 the mental state was uncertain, and that only 11 appeared definitely mentally normal.

One thing upon which all can agree is that most of these premature infants needed oxygen at birth, because of their anoxic state.

With regard to spastic diplegia, as Ford (1952) has emphasized, a number of writers have stressed the importance of asphyxia at birth, although, as he points out, it is a difficult factor to evaluate since many babies are deeply asphyxiated without ill-effects.

In 1952, Hepner and Krause pointed out that cow's milk contained four times the sodium, twice the chloride, and seven times the phosphorus content of human milk. They stressed the fact that early feeding with cow's milk mixtures might result in an electrolyte retention and imbalance. This, in turn, would result in generalized œdema which might also affect the retina.

However, Coxon (1951) and Crosse (1951) have reported the occurrence of retrolental fibroplasia in infants who have been totally fed on breast milk.

It would seem clear, therefore, that, if cow's milk is at fault, it can only be an exacerbating factor and not the primary cause of the retinal changes.

In the light of our present knowledge, therefore, my own feeling regarding the retinopathy of prematurity is that it is a part of a general cerebral disorder resulting primarily from anoxæmia. On the other hand, I think that it may well be that the administration of prolonged oxygen, by superadding retinal vasoconstriction with consequent transudation into the layers of the retina, aggravates the initial angioblastic disturbance and may therefore, in fact, be responsible for the high incidence of the condition in recent years although not the primary factor in the ætiology of the underlying pathological disturbance.

I would like to express my indebtedness to Dr. J. D. Kerr, in conjunction with whom I carried out the survey of children with retrolental fibroplasia, and I am also indebted to Dr. T. T. S. Ingram for permission to publish the photograph of the child with retrolental fibroplasia and severe diplegia.

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Dr. S. P. Meadows: Failure of vision in childhood, as in adults, has many facets. The possible pitfalls in diagnosis are numerous. A patient of my own, a boy in his teens, was saved from ventriculography largely by a letter from an oculist, who reported that the optic discs had appeared swollen several years previously, and subsequent events upheld the diagnosis of pseudo-papillœdema. At the other extreme are the patients who present with near blindness and little to show on examination, except, perhaps, poorly reacting pupils. The patient is blind and the physician may see nothing, and there may be a danger of attributing the blindness to a manifestation of hysteria. Loss of function may precede visible ophthalmoscopic changes when the optic nerves or chiasm are compressed, as, for example, by a craniopharyngioma, or in cases of retrobulbar neuritis. In case of cortical blindness the fundus oculi and pupils may be entirely normal.

The examination of children has, of course, its own peculiar difficulties. Who has not marvelled at the strength of the eye closure muscles, the orbicularis oculi, in a child, during examination of the fundus oculi? Or prayed that the wandering eyes might develop a momentary loss of conjugate movements, preferably in all directions, when the optic disc comes into view for a fleeting moment

Papillœdema

Papillœdema in childhood, as in adults, is commonly associated with an intracranial tumour. It is, however, sometimes due to increased intracranial pressure consequent on aqueduct stenosis, and occasionally appears as a complication of a local infection, usually otitis. It is, of course, seen in meningitis, and I am sure many of us have had the experience of diagnosing an intracranial tumour in an ill-looking patient who walks into the out-patient department, and who is actually the subject of tuberculous meningitis. Severe papillœdema, due to increased intracranial pressure from any cause, is, of course, often present with relatively normal vision. Later, however, visual failure may appear, in association with secondary optic atrophy, and, if visual failure has already commenced, relief of intracranial pressure by operative procedures does not always arrest it: a point of some importance in prognosis.

I wish to say little about papillœdema due to intracranial tumours, except to refer to the fact that it is often absent in the fairly common pontine glioma in childhood. In these cases, gradual loss of function may appear, including ocular and cranial nerve palsies, and signs of pyramidal involvement, with a progressive deterioration in the patient's condition, while the optic fundi remain quite normal, even until a few days before death. A patient of my own, a child aged 5 years, developed an isolated third cranial nerve palsy with no other symptoms or signs, and after a period of eighteen months a contralateral hemiplegia appeared, suggesting a lesion in the neighbourhood of the crus cerebri. The optic fundi remained entirely normal. At autopsy a large glioma was present in the pons and invading the mid-brain, and a mass of tumour had protruded from the brain-stem and surrounded the III nerve, giving rise to a clinical picture which led us to suspect a lesion outside rather than inside the brain-stem.

The only other clinical feature to which I would call attention is the case of a patient who presents with papillœdema and other features suggesting increased intracranial pressure, but with impairment of vision more severe than would be expected from the degree of papillœdema. In one patient, a child of 5 years, rapidly failing vision, papillœdema and an ataxic gait suggested the presence of a posterior fossa tumour. But visual acuity was severely affected, much more so than would be warranted by the appearance of the optic fundi, although no local field defect could be discovered. Further investigation showed the presence of a large craniopharyngioma, and it may be that her ataxia was partly due to her poor vision. This combination of severe loss of vision with only a moderate degree of swelling of the optic discs is suggestive of a basally situated tumour, such as a craniopharyngioma, which is compressing the optic nerves and chiasm as well as causing increased intracranial pressure. But a somewhat similar clinical picture may be caused by bilateral retrobulbar neuritis.

Papillœdema is also seen in childhood, as in adult life, with clinical features suggestive of an intracranial tumour, and on ventriculography the ventricular system is found to be of normal configuration, or the lateral ventricles may even be small and symmetrical. In childhood, this syndrome is often associated with an infective process, especially otitis, and at one time the term otitic hydrocephalus was used. It is thought that these cases may be associated with thrombosis of intracranial veins, especially the lateral sinus or superior sagittal sinus. In other cases, however, and more especially in adults, no focus of infection is present, and we are uncertain of the exact pathology. Visual failure may appear in these cases, perhaps more commonly in the cases unassociated with local infection, and consecutive optic atrophy with considerable impairment of vision may be the final state. On the other hand, many of these cases, and particularly those associated with otitis in childhood, appear to progress favourably. The papillœdema subsides leaving vision intact, after only a short period of repeated lumbar puncture.

A child I saw in 1938, aged 12 years, developed severe papillœdema during the course of an acute infection of the ear and mastoid, without other neurological signs. In spite of the infection, the child did not appear ill and was quite alert. Lumbar puncture showed a raised pressure but a normal fluid. The child made a fairly rapid recovery after several lumbar punctures, and was seen eight years later fit and well, with normal vision.

It seems probable that the treatment of choice in these cases, once the diagnosis is assured—and air pictures being normal—is that of repeated lumbar puncture. The latter is not entirely devoid of risk, however, for the presence of cerebral œdema may behave in a way like a tumour, and lead to herniation of the temporal lobes into the incisura of the tentorium, and of the cerebellar tonsils into the foramen magnum. Withdrawal of fluid should therefore be performed with caution, and the pressure should not be allowed to fall below about 150 mm. Lumbar puncture should not be repeated for at least twenty-four hours, as too frequent drainage may cause considerable disturbance and even precipitate a fatality. The desirability of subtemporal decompression needs to be considered in some of these cases with persistent papillœdema or failing vision.

Aqueduct stenosis is also a condition which gives rise to increased intracranial pressure with papillœdema in children. It is really a ventriculographic diagnosis, with dilated lateral and third ventricles and a block above the fourth ventricle.

A recent case of this disorder, a girl aged 5 years, had a history of increasing unsteadiness on the legs for eighteen months, together with slight unsteadiness of the arms. She had never complained of headaches. Examination revealed a large head, severe papillœdema, ataxia of all four limbs and

bilateral extensor plantar responses. A clinical diagnosis of cerebellar astrocytoma was rebutted by the air pictures which showed a block in the aqueduct. Following a Torkildsen's operation, with drainage of the lateral ventricles into the posterior fossa, there was a gradual improvement, so that nine months after operation she was back at school, still slightly ataxic, and with pallor of both discs and fair vision.

Tumours Involving the Optic Nerves and Chiasm

Compression of the chiasm and of the optic nerves is a cause of visual failure in adults and in childhood, though the compressing agent varies to some extent with the age period. In adult life meningiomas and pituitary adenomas are common, but they are rare in childhood. The two tumours which present themselves particularly in childhood, though they are by no means limited to this age group, are the gliomas of the optic nerve and chiasm, and the tumours of Rathke's pouch or craniopharyngiomas.

A glioma of the optic nerve is sometimes a relatively benign tumour, at least from the clinical point of view. It is thought that these tumours usually arise from the intra-orbital portion of the optic nerve and less commonly from the intracranial portion, though at operation it is often difficult to be certain of the point of origin. In many cases intracranial extension occurs through the optic foramen, and the tumour may reach the chiasm or beyond.

The clinical features are, perhaps, too well known to need further description. Unilateral visual failure is followed by proptosis, which is usually axial and irreducible. Ocular movements are frequently preserved, at least in the early stage, and pain is not usually a prominent feature. The optic disc is usually atrophic, but a recent case under my care, however, a girl of 15 years, presented with severe unilateral papillœdema, and vision reduced to hand movements in the nasal field. Had it not been for slight exophthalmos, a diagnosis of retrobulbar neuritis might have been considered. In another patient, an adult, thrombosis of the central retinal vein was the first sign of an optic nerve glioma, a most unusual mode of presentation. The patient later developed secondary glaucoma in this eye, but it was only when vision began to fail in the temporal field of the good eye that the question of a tumour was considered. Operation revealed a glioma involving both optic nerve and chiasm, which had spread backwards to the brain-stem.

Enlargement of the optic foramen on radiography is one of the important diagnostic signs, and is indicative of intracranial extension. Cases have been recorded of invasion of the optic disc, with a visible swelling seen on ophthalmoscopy.

The prognosis varies a good deal from case to case, but some of these tumours are of slow growth, and the patient may live for many years after removal, even when the removal has been incomplete. A case I first saw in 1939, and whose optic nerve was removed by Mr. Wylie McKissock as far back as the chiasm, is still alive and well, the vision in the other eye remaining good.

The onset of symptoms occurs before puberty in by far the majority of cases, but they are occasionally seen in adult life. The rare association with von Recklinghausen's neurofibromatosis is well known.

Gliomas involving the chiasm also tend to occur in childhood, though not confined to this age group. A glioma of the optic nerve may spread back to involve the chiasm, but it seems likely that the chiasm itself is sometimes the primary seat of a glioma. Martin and Cushing were among the first to call attention to this group of gliomas, which were often surprise findings at operation. There is usually a fairly rapid and progressive loss of vision which may be asymmetrical in the two eyes. The patient often presents with blindness of one eye, but the other eye usually has impairment of vision. A defect in the temporal field, which may not show a clean vertical bisection, is a feature, together with bilateral optic atrophy. Exophthalmos may appear at an advanced stage. Endocrine disturbance is unusual, at least to any marked degree, and radiological examination may be negative, though excavation under the clinoid processes may be seen. It is clear that differential diagnosis in these cases is from a craniopharyngioma, which is usually associated with radiological evidence of damage to the sella or suprasellar calcification. Operative treatment has little to offer in these cases, and the results of radiotherapy are problematical.

Meningioma of the optic nerve sheath is a tumour of adult life, and presents with clinical features similar to those of a glioma, i.e. unilateral visual failure with exophthalmos, though defects in ocular movements may also be present. These tumours are rare enough in adults, and must be excessively rare in childhood. Walsh records a case in a child of 8 years, however. The youngest patient I have seen with this condition was a girl who started to lose the sight of the right eye at the age of 17 years. Within three years she was virtually blind in this eye, with optic atrophy and slight exophthalmos. The vision in the remaining eye then began to deterioate, though a year later the vision in this eye was still 6/12, and there was no localized defect in the field. All investigations were negative including radiographic examination of the skull and optic foramina, and examination of the cerebrospinal fluid, and arteriography and air pictures showed no definite abnormality. On exploration, at the age of 28, and eleven years after the onset of symptoms, a small cuff of tumour was found surrounding each optic nerve, two quite separate meningiomas of the optic nerve sheaths. Radical treatment was unfortunately impossible. The negative investigations are of some interest

after a period of over ten years. Occasionally the cuff-like meningioma surrounding the optic nerve in the orbit is merely a small extension of a large intracranial meningioma, which may be clinically silent.

Tumours of Rathke's pouch (craniopharyngioma) are one of the commoner causes of compression of the chiasm and optic nerves in childhood. Although *par excellence* a tumour of childhood, a graph of their age incidence tapers off gradually towards middle age. They are sometimes encountered in the forties and fifties, perhaps when a chromophobe tumour has been expected. For a craniopharyngioma can arise inside the sella and mimic a pituitary adenoma to a nicety, even at operation. In children, loss of vision is, as a rule, more gradual than in the chiasmal gliomas, and a clean-cut defect in the temporal fields more likely. Papillœdema may be seen in childhood, but is rare in adults, when optic atrophy is the rule. The combination of bitemporal hemianopia and papillœdema in a child is rarely due to any other cause. Examination of the visual fields is sometimes impossible in children, but perhaps the combination of visual failure in excess of what might be expected from the degree of papillœdema should direct our thoughts to a craniopharyngioma, or to retrobulbar neuritis. Endocrine dysfunction is common, including delayed skeletal and sexual development, and the child retains his boyish appearance after puberty. Radiographic changes are present in most cases, with destruction of the sella, calcification above the sella, and signs of increased intracranial pressure. These tumours may grow to a very large size, with cystic extensions as far back as the pons, or invading the frontal or temporal lobes, so that radical surgery is frequently impossible.

Pituitary adenomas, a common cause of visual failure in adults, are very rare in childhood. I have had one patient, whose symptoms started at the age of 15 years with periodic headaches. She was first examined at the age of 17 years, when there was an incomplete bitemporal field defect on testing on the Bjerrum screen, with normal optic fundi, and good central vision. The breasts were undeveloped and the patient had never menstruated. Radiographic examination showed a ballooned sella, suggestive of a chromophobe adenoma, and this, indeed, proved to be the case at operation. She had a twin sister who acted as an excellent control, both from the endocrine and radiological aspects.

Retrobulbar Neuritis

Unilateral retrobulbar neuritis, so commonly seen in adults, either as an isolated event or during the course of frank disseminated sclerosis, is rarely seen under the age of 15 years. On the other hand, bilateral retrobulbar neuritis, though uncommon, is a well-recognized entity in childhood. It may appear abruptly in a child previously in good health, or following a period of vague ill-health lasting some weeks, or following chickenpox and measles. An abrupt onset of loss of vision, sometimes almost complete blindness, or gross loss of central vision, is accompanied by blurring or frank swelling of both optic discs. In 6 out of 9 such cases seen during the past few years, all children between the ages of 5 and 10 years, there were no other signs of involvement of the central nervous system. Recovery of vision is the rule, within a few weeks, though the child may be left with pale optic discs. Most of the children were able to return to school and lead a normal life. 2 of the 9 children so affected had evidence of pyramidal involvement which later disappeared. The differential diagnosis from an intracranial tumour can be one of considerable difficulty, and ventriculography may be necessary. It was performed in 2 of these 9 cases.

That such an episode may be followed by freedom from further symptoms for many years is shown by 3 further patients seen in adult life, aged 26, 34 and 55 years, all of whom gave a history of abrupt loss of vision in both eyes at the ages of 8, 9 and 5 years, respectively. All 3 patients had optic atrophy, and 2 of them had only slight impairment of vision. The third patient, seen at the age of 55, fifty years after the initial episode, had been left with gross impairment of vision, severe enough to be certifiable as blind, but was otherwise healthy and active.

Affections of the Optic Radiations and Visual Cortex

Affections of the optic radiations and visual cortex are perhaps less common in childhood than in adult life. In adults, vascular lesions and neoplasms of the cerebral hemispheres are amongst the commoner causes of hemianopic field defects, but are relatively uncommon in childhood. On the other hand, demyelinating diseases, such as the Schilder group, are seen particularly in young subjects, and various forms of encephalitis may affect the visual pathways, such as subacute inclusion encephalitis (Dawson).

Vascular lesions.—Homonymous hemianopia of abrupt onset, without hemiplegia, is a common enough event in middle-aged or elderly patients, usually due to thrombosis of the calcarine artery, but is rarely encountered in childhood. Thrombosis of the internal carotid artery, however, though usually appearing in middle age, has been recorded in patients in their teens. In this condition, fleeting premonitory symptoms may occur for weeks or months before the sudden onset of a contralateral hemiplegia, and include contralateral hemiparesis or sensory symptoms, and dysphasia. A premonitory symptom of some interest is that of temporary loss of vision in the ipsilateral eye, due to retinal ischæmia, and yet a permanent loss of vision in this eye is unusual, even when a severe hemiplegia finally appears, and this is presumably due to an adequate collateral circulation through branches of the external carotid artery. Cerebral embolism may, of course, appear as a complication of bacterial endocarditis, and the development of mycotic aneurysms is not unusual. The territory

of the middle cerebral artery is commonly affected, with the abrupt onset of hemiplegia, often in association with a homonymous defect in the contralateral visual fields. A mycotic aneurysm may also cause visual symptoms. Ford describes a child of 9 years, who developed a mycotic aneurysm of the posterior cerebral artery, which compressed the III cranial nerve, and it seems feasible that a sudden homonymous hemianopia might arise from a mycotic aneurysm so situated, either by leakage into brain substance, or obstruction of the artery.

Intracranial tumours involving the cerebral hemispheres are relatively uncommon in childhood, compared with the older age groups, and we are, perhaps, inclined to regard them as rarities. When the angiomas are excluded, the gliomas form the bulk of the remainder, though several meningeal tumours are described by Bailey, P., Buchanan, D. N., and Bucy, P. C., in their book on "Intracranial Tumours in Infancy and Childhood", Chicago, 1939.

I should like to refer briefly to 3 children with gliomas involving the cerebral hemisphere, all of whom presented with impairment of vision. Neither of the first 2 patients had complained of headache. In the first case the optic nerves were involved by a frontal lobe glioma, an unusual event at any age. Basal meningiomas are so placed, of course, that they frequently do so.

Case I.—Large right frontal cystic astrocytoma, involving the optic nerves.

A boy, aged 4 years, presented with a history of rapid failure of vision in both eyes over a period of three months. Headaches were insignificant, and the child remained alert and active. He was blind in one eye, and had only perception of light in the other, with bilateral optic atrophy, but no other signs in the central nervous system. An interesting feature was the rapidity with which this virtually blind child familiarized himself with his environment by touch. He rapidly fingered his bed and his locker, and appeared to have adjusted to his visual loss in a remarkable fashion. Ventriculography showed a large filling defect in the anterior horn of the right lateral ventricle, and on needling a large cyst was encountered. Operation revealed a very large right frontal cyst, which had invaded the temporal lobe and both optic nerves, and proved to be a cystic astrocytoma.

Case II.—Cystic astrocytoma of right cerebral hemisphere in a girl aged 11, with cutaneous manifestations of neurofibromatosis.

This girl, who had typical cutaneous neurofibromatosis, complained of recent impairment of vision, especially to the left side, so that she bumped into objects on her left side, and she had noticed impairment of sensation in her left foot. She had not complained of headaches. Examination showed a left homonymous hemianopic defect, pallor of both optic discs and minimal left-sided pyramidal signs. Ventriculography revealed a large tumour in the right cerebral hemisphere, and operation revealed a large cyst, with a mural nodule, which was removed. Histology showed this to be an astrocytoma.

There has been no clinical evidence of recurrence during the three and a half years following operation. The hemianopic defect and hemiparesis have persisted, but the child is able to lead a fairly active life.

Case III.—Calcified right occipital cystic astrocytoma in a child of 12 years.

This girl had complained of right-sided headache for a year, without other symptoms. Examination revealed bilateral papillœdema, and a lower left quadrantic homonymous defect in the visual fields, with no other abnormal signs. Radiography showed an area of calcification in the right occipital lobe, which proved to be cystic on air studies. Amputation of the right occipital lobe was performed by Mr. McKissock. The child is quite well two and a half years after operation, and is attending school. There is a complete left homonymous hemianopia extending to fixation, but the patient notices no disability from this.

Intracranial angioma.—Intracranial angiomas are sometimes seen in childhood and in young adults, and are prone to cause visual defects from affection of the optic radiations. In Mackenzie's recent series of 50 proved intracranial angiomas, for instance, over 50% started with symptoms in the first two decades, and in 10% symptoms started under the age of 10 years.

As is well known, these tumours are vascular malformations rather than true tumours, and the vast majority are situated in the cerebral hemisphere, and predominantly in the territory of the middle cerebral artery. Although the mode of presentation is commonly by an increasing hemiplegia, with exacerbations, or by focal or generalized epileptiform attacks, other modes of presentation are of interest.

A cerebral angioma may present with a clinical history suggesting migraine, as in the following patient, a male aged 40.

Since the age of 9 years he had suffered from attacks at intervals of a few weeks. An attack was heralded by sudden visual hallucinations, consisting of stars and flashing lights, usually pink and white in colour, and always situated to the left of the mid-line, in the left homonymous fields. After fifteen to thirty minutes the visual symptoms subsided, and were followed by a severe right-sided headache and vomiting, lasting for some hours. The attacks became less frequent during the past few years, and were replaced by attacks of mistiness in the left homonymous fields, and occurring up to two or three times a day, and not followed by a headache. There have been no epileptic attacks, and his general health has been unaffected. Examination revealed a lower left homonymous quadrantic field defect, with normal fundi and no other signs on neurological examination. A cephalic murmur was audible in the right suboccipital region, and a thrill was palpable, due to a mass of pulsating vessels outside the skull. Compression of the right common carotid artery in the neck abolished the bruit. It is of interest that the bruit was hardly audible on auscultation over the eye or in the temporal region.

Although these patients are often first seen in adult life, symptoms usually start in youth, under the age of 20. The recurrent headache is usually confined to the side of the angioma, the visual symptoms are persistently in the opposite homonymous fields, and a bruit is usually present by the time the patient presents himself to the physician. Recurrent epileptic attacks may occur during the clinical

course. This mode of presentation of cerebral angioma is, of course, well recognized. Adie discussed cases with this type of symptomatology as long ago as 1930.

Subarachnoid hæmorrhage, particularly in young subjects, is sometimes due to a cerebral angioma, which may have been previously symptomless, as in the following case.

A girl, aged 8 years, was admitted to the National Hospital, Queen Square, with a history of having been taken suddenly ill at school two weeks previously. Headache and vomiting of abrupt onset were followed by signs suggestive of subarachnoid hæmorrhage, and this was proved by the finding of a blood-stained fluid on lumbar puncture. The patient gradually improved, and on admission to the National Hospital, two weeks after the onset of symptoms, she had almost fully recovered. There were no abnormal signs on examination except a right-sided upper quadrantic homonymous field defect, with good central vision and normal optic fundi. There was no cephalic bruit. A left carotid arteriogram was normal, though the posterior cerebral artery did not fill. Vertebral arteriography, however, showed an angioma in the occipital region. Presumably there had been an intracerebral leak, as well as subarachnoid bleeding, as also frequently occurs in cases of intracranial aneurysm. The patient was fit and well a year after the subarachnoid hæmorrhage, though the field defect persisted.

In another patient, a girl aged 16, who presented with subarachnoid hæmorrhage, and whose father died of a subarachnoid hæmorrhage, angiography later showed a large angioma in the parietal region, and air pictures showed that the angioma was deforming the lateral ventricle. There was no cephalic bruit, nor indeed any residual signs, and the patient has been symptomless and living a normal life for three and a half years since the subarachnoid hæmorrhage.

From these 2 patients, aged 8 and 16, one may conclude that subarachnoid hæmorrhage in childhood may be associated with an angioma rather than an aneurysm, that an audible cephalic bruit, formerly regarded as an integral part of the clinical picture in angiomas, may be absent, that carotid arteriography may be negative, if the angioma arises in the territory of the posterior cerebral artery, and that the angioma may be seated so deeply as to cause deformation of the lateral ventricle. The absence of a cephalic bruit in cases of angioma which present with subarachnoid hæmorrhage has already been commented upon by Mackenzie, and may be due to the depth of the angioma.

In conclusion, it is of interest that several conditions causing blindness in childhood in the past are now a rarity. As for example, congenital syphilis, gonococcal ophthalmia, and the ocular sequelæ of acute infections. It is perhaps even more interesting to speculate on the form which such a discussion on visual failure in childhood may take, say, fifty years hence: when, perhaps, there will be no infection which cannot be controlled in its early stages, and when the biochemist or pathologist has solved the riddle of demyelination, and possibly even tumour formation.

Dr. J. G. Greenfield: I propose to confine my remarks to the pathology of two forms of disease in children: (1) the cerebrospinal lipidoses, and (2) so-called diffuse scleroses of the brain, or Schilder's disease.

(1) In the lipidoses blindness is due to degeneration of the retina, but this is not always of the same type. There appear to be two fairly distinct forms, clinically differentiated by the presence or absence of a cherry-red spot at the macula. In those without this spot there may be pigmentary changes either in the zone round the macula or more widely in the retina. The form with a cherry-red spot is usually called after Tay and Sachs who first described it. I was glad to find that Mr. Doggart (1947) had called the second form, the Batten type, since Dr. Frederick Batten, who, in his day, had an unrivalled knowledge of the nervous diseases of childhood, well deserves this honour to his memory. In Germany it is often called the Vogt-Spielmeyer type, as it was described by these authors during the two years which followed Batten's description in 1903:

(*a*) The changes in the retina in cases of the Tay-Sachs type are well established. In my small experience they are the same whether the patient is Jewish or not, and whether the disease comes on during the first year of life or later, even up to the third year. I have had the opportunity of examining the retina in 3 children with no known Jewish heredity. One died at the age of 18 months, the other two, a brother and sister, at the ages of 2 11/12 and 3 9/12 years. In all 3 the nerve cells contained an excess of lipoid, and were fewer than normal, as was most easily seen close to the macula; but there was no abnormality in the outer nuclear layer, the rods and cones or the pigmented epithelium. In some of these, but not in all, the fovea centralis appeared to be wider than normal, but as fixative was injected into the vitreous under pressure, this appearance may have been due to artefact.

(*b*) In the cases of Batten type without a cherry-red spot, the nerve cells are less affected, though they may not be entirely normal. The chief change here is in the outer nuclear layer and the pigmentary epithelium. The outer nuclear layer degenerates and disappears, apparently first, in a zone round the macula. The rods and cones, of course, go with this layer and pigment from the epithelium migrates into the outer molecular layer. In later cases, in which pigmentary degeneration of the retina is visible ophthalmoscopically, the outer nuclear layer may have disappeared over wide areas of the retina.

I have examined the retina in 4 cases of this kind, 2 aged 4 and the others 9 and 15 years at the time of death. There is therefore practically no gap in age between the oldest with a cherry-red spot and the youngest without one. On the other hand there is no overlap in my material. There is very little evidence of transition from one type to the other. A case of Tay-Sachs type may be totally blind for

months and yet show no gap in the outer nuclear layer, whereas a case of the Batten type may not be noticeably blind at the time of death, and yet the gap in the outer nuclear layer may be very evident. It would appear that there is an essential difference in pathogenesis in the two conditions, but it is difficult to make out exactly what this is.

(2) *Diffuse sclerosis of the brain.*—The terms diffuse sclerosis of the brain and Schilder's disease cover several different forms of degeneration of the cerebral white matter, some of which are usually familial, but in others there is less evidence of hereditary transmission. So far as my reading of the literature has gone, blindness in children suffering from these conditions has always been due to degeneration of the occipital white matter. The optic nerves have only been affected in a few adult cases; but I see no reason why there should be any restriction of this kind, in view of the close pathological similarity between certain forms of diffuse cerebral sclerosis and Devic's disease, neuromyelitis optica.

I recently suggested that cases of diffuse cerebral sclerosis shall be classified into three main groups according to their pathogenesis: (1) The sudanophilic group in which the lipoid metabolism follows a pattern similar to that seen in disseminated sclerosis. This group may be familial, and blindness is a common, though not constant, early symptom. (2) The metachromatic group, rarely familial, in which there is little or no sudanophilic lipoid, but granules of cerebrosides collect in phagocytic cells, and metachromatic lipoid may also be found in the liver and kidneys. In this group the optic radiations tend to be spared and therefore blindness, if it occurs at all, comes on late in the disease. (3) A curious familial type characterized by the presence of collections of globoid or epithelioid cells which do not contain sudanophilic lipoid. Blindness may be an early sign in such cases, but here also it is not constant.

I do not think that it is possible to distinguish clinically between types (1) and (3), but cases of type (2) are, in my experience, characterized by early cerebellar symptoms and signs and by absence of blindness. It seems to me that these three types, if not quite distinct, are at least separable on the grounds of pathology and pathogenesis. In the very slowly progressive familial type called after Pelizaeus and Merzbacher there is rarely blindness, as here, too, the optic radiations tend to survive longer than other parts of the white matter.

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Sir Stewart Duke-Elder said that he would like to comment briefly on retrolental fibroplasia (or) as it would be much more happily called, the retinopathy of prematurity) and particularly its association with spastic defects. At the moment the disease was relatively common. In 1951 statistics gathered through the Ministry of Health showed that there were 126 cases among premature infants born at weights of less than 4½ lb. in England and Wales—a distressing fact socially and a heavy burden economically in terms of blind pensions. All these cases occurred in hospitals. It was also a fact now that among the cases which found their way into the Sunshine Homes for blind babies some 20% were mentally deficient and a further 30% were mentally retarded; it would thus appear that 50% of these children had suffered some cerebral trauma, probably in the sense of anoxia. He thought that Mr. Scott might have misinterpreted Norman Ashton's pathological findings. It was true that in Ashton's experiments on kittens, neovascularization followed most readily after the administration of oxygen in the few days following birth; it was, however, not certain that the oxygen itself caused the pathological changes, but very probable that it caused an obliteration of the circulation leading to anoxia which presumably was the ætiological factor. The administration of oxygen soon after the birth of a kitten was the easiest way to bring about anoxia. It might well be the case that sporadic instances of retrolental fibroplasia occurred without the administration of oxygen, but it would seem obvious that there were other potential mechanisms, for example *in utero*, which could cause a condition of anoxia.

It is interesting that a survey of a number of nurseries for premature babies in this country has shown that the incidence of this disease varied directly with the amount of the oxygen used, and in those centres wherein the administration of oxygen has been cut down and adequately supervised, the condition has practically disappeared. This corresponds with American experience. From the practical point of view, it would seem that the retinopathy of prematurity is a preventable condition and rarely occurs provided oxygen is given to premature children (particularly between the weights of 2½ and 3 lb.) only in the smallest quantities and for the shortest time necessary to avoid respiratory embarrassment.